DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Memorandum

Date FEB - 7 1997

From Director, Office of Device Evaluation (HFZ-400)
Center for Devices and Radiological Health (CDRH)

Subject Premarket Approval of Medtronic, Inc. Legend Plus® Pacing System- ACTION

To The Director, CDRH
ORA _____

ISSUE. Publication of a notice announcing approval of the subject PMA.

FACTS. Tab A contains a FEDERAL REGISTER notice announcing:

(1) a premarket approval order for the above referenced medical device (Tab B); and

(2) the availability of a summary of safety and effectiveness data for the device (Tab C).

RECOMMENDATION. I recommend that the notice be signed and published.

Susan Alpert, Ph.D., M.D.

Attachments
Tab A - Notice
Tab B - Order
Tab C - S & E Summary

DECISION

Approved _____ Disapproved _____ Date _____

Prepared by Mitchell Shein, CDRH, HFZ-450, 11/8/96, 443-8517

DRAFT

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

[DOCKET NO. _____]

Medtronic, Inc.; PREMARKET APPROVAL OF the Legend Plus® Pacing System

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing its approval of the application by Medtronic, Inc., Minneapolis, MN, for premarket approval, under the Federal Food, Drug, and Cosmetic Act (the act), of the Legend Plus® Pacing System. After reviewing the recommendation of the Circulatory System Devices Panel, FDA's Center for Devices and Radiological Health (CDRH) notified the applicant, by letter on February 7, 1997, of the approval of the application.

DATES: Petitions for administrative review by (insert date 30 days after date of publication in the FEDERAL REGISTER).

ADDRESSES: Written requests for copies of the summary of safety and effectiveness data and petitions for administrative review, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

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FOR FURTHER INFORMATION CONTACT:

Mitchell J. Shein,

Center for Devices and Radiological Health (HFZ-450),

Food and Drug Administration,

9200 Corporate Blvd.,

Rockville, MD 20850,

301-443-8517.

SUPPLEMENTARY INFORMATION: On July 21, 1993, Medtronic, Inc., Minneapolis, MN, 55432, submitted to CDRH an application for premarket approval of the Legend Plus® Pacing System consisting of the following components: the Legend Plus® Pulse Generator Models 8446 and 8448; the Model 9790 and 9790C Programmers with the Model 9891 Baseline Software and the Model 9807 Software. The device system includes implantable pulse generators and associated programming hardware and software and is indicated for permanent ventricular or atrial pacing applications. Their use is indicated in the treatment of patients who may benefit from a pacing rate that changes in response to activity.

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Ventricular indications include:

- chronic atrial flutter or fibrillation with slow ventricular response;
- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, chronotropic insufficiency, etc.,); and
- AV block

Atrial indications include:

- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, etc.,) with intact AV conduction.

On May 9, 1995, the Circulatory System Devices Panel of the Medical Devices Advisory Committee, an FDA advisory committee, reviewed and recommended approval of the application.

On February 7, 1997, CDRH approved the application by a letter to the applicant from the Director of the Office of Device Evaluation, CDRH.

A summary of the safety and effectiveness data on which CDRH based its approval is on file in the Dockets Management Branch (address above) and is available from that office upon written request. Requests should be identified with the name of the device and the docket number found in brackets in the heading of this document.

Opportunity For Administrative Review

Section 515(d)(3) of the act (21 U.S.C. 360e(d)(3)), authorizes any interested person to petition, under section 515(g) of the act, for administrative review of CDRH's decision to approve this application. A petitioner may request either a formal hearing under part 12 (21 CFR part 12) of FDA's administrative practices and procedures regulations or a review of the application and CDRH's action by an independent advisory committee of experts. A petition is to be in the form of a petition for reconsideration under §10.33(b) (21 CFR 10.33(b)). A petitioner shall identify the form of review requested (hearing or independent advisory committee) and shall submit with the petition supporting data and information showing that there is a genuine and substantial issue of material fact for resolution through administrative review. After reviewing

the petition, FDA will decide whether to grant or deny the petition and will publish a notice of its decision in the FEDERAL REGISTER. If FDA grants the petition, the notice will state the issue to be reviewed, the form of the review to be used, the persons who may participate in the review, the time and place where the review will occur, and other details.

Petitioners may, at any time on or before insert date 30 days after date of publication in the FEDERAL REGISTER), file with the Dockets Management Branch (address above) two copies of each petition and supporting data and information, identified with the name of the device and the docket number found in brackets in the heading of this document. Received petitions may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

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This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 515(d), 520(h), (21 U.S.C. 360e(d), 360j(h))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Director, Center for Devices and Radiological Health (21 CFR 5.53).

Dated:_____.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

FEB - 7 1997

Mr. Patrick L. Johnson
Product Regulation Manager
Medtronic, Inc.
7000 Central Avenue, N.E.
Minneapolis, Minnesota 55432-3576

RE: P930022
Legend Plus® Pacing System
Filed: July 21, 1993
Amended: June 16 and September 21, 1994; March 1 and 27, June 15, September 1, 13, and 14, and November 14, 1995; January 16, April 12, August 5, September 12 and 24, October 25, and November 8, 1996; and January 21, 1997

Dear Mr. Johnson:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the Legend Plus® Pacing System including the Legend Plus® Pulse Generator Models 8446 and 8448; the Model 9790 and 9790C Programmers with the Model 9891 Baseline Software and with the Model 9807 Software. This system is indicated for permanent ventricular or atrial pacing applications. Its use is indicated in the treatment of patients who may benefit from a pacing rate that changes in response to activity.

Ventricular indications include:

- chronic atrial flutter or fibrillation with slow ventricular response;
- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, chronotropic insufficiency, etc.,); and
- AV block.

Atrial indications include:

- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, etc.,) with intact AV conduction.

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We are pleased to inform you that the PMA is approved subject to the conditions described below and in the "Conditions of Approval for Cardiac Pacemakers and Programmers" (enclosed). You may begin commercial distribution of the device upon receipt of this letter.

The sale, distribution, and use of this device are restricted to prescription use in accordance with 21 CFR 801.109 within the meaning of section 520(e) of the Federal Food, Drug, and Cosmetic Act (the act) under the authority of section 515(d)(1)(B)(ii) of the act. FDA has also determined that to ensure the safe and effective use of the device that the device is further restricted within the meaning of section 520(e) under the authority of section 515(d)(1)(B)(ii) insofar as the sale, distribution, and use must not violate sections 502(q) and (r) of the act.

Expiration dating for this device has been established and approved at 18 months.

CDRH will publish a notice of its decision to approve your PMA in the FEDERAL REGISTER. The notice will state that a summary of the safety and effectiveness data upon which the approval is based is available to the public upon request. Within 30 days of publication of the notice of approval in the FEDERAL REGISTER, any interested person may seek review of this decision by requesting an opportunity for administrative review, either through a hearing or review by an independent advisory committee, under section 515(g) of the act.

Failure to comply with the conditions of approval invalidates this approval order. Commercial distribution of a device that is not in compliance with these conditions is a violation of the act. You are reminded that as soon as possible, and before commercial distribution of your device, that you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form.

All required documents should be submitted in triplicate, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

PMA Document Mail Center (HFZ-401)
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Boulevard
Rockville, Maryland 20850

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In addition under section 522(a) of the act, manufacturers of certain types of devices identified by the act or designated by FDA are required to conduct postmarket surveillance studies. FDA has identified under section 522(a)(1)(A) the above noted device as requiring postmarket surveillance.

Upon approval and within thirty (30) days of first introduction or delivery for introduction of this device into interstate commerce you will be required to submit to FDA certification of the date of introduction into interstate commerce, a detailed protocol which describes the postmarket surveillance study, and a detailed profile of the study's principal investigator that clearly establishes the qualifications and experience of the individual to conduct the proposed study. For your information, general guidance on preparing a protocol for a postmarket surveillance study is enclosed.

At that time you should submit five (5) copies to:

Postmarket Studies Document Center
1350 Piccard Drive (HFZ-544)
Rockville, Maryland 20850

Within sixty (60) days of receipt of your protocol, FDA will either approve or disapprove it and notify you of the Agency's action in writing. Do not undertake a postmarket surveillance study without an FDA approved protocol.

Failure to certify accurately the date of initial introduction of your device into interstate commerce, to submit timely an acceptable protocol, or to undertake and complete an FDA approved postmarket surveillance study consistent with the protocol, will be considered violations of section 522. In accordance with the Medical Device Amendments of 1992, failure of a manufacturer to meet its obligations under section 522 is a prohibited act under section 301(q)(1)(C) of the act (21 U.S.C. 331(q)(1)(C)). Further, under section 502(t)(3) of the act (21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the act. Violations of sections 301 or 502 may lead to regulatory actions including seizure of your product, injunction, prosecution, or civil money penalties or other FDA enforcement actions including (but not limited to) withdrawal of your PMA.

If you have any questions concerning postmarket surveillance study requirements, contact the Postmarket Surveillance Studies Branch, at (301) 594-0639.

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Under section 519(e) of the act (as amended by the Safe Medical Devices Act in 1990), manufacturers of certain devices must track their products to the final user or patient so that devices can be located quickly if serious problems are occurring with the products. The tracking requirements apply to (1) permanent implants the failure of which would be reasonably likely to have serious adverse health consequences; (2) life sustaining or life supporting devices that are used outside of device user facilities the failure of which would be reasonably likely to have serious adverse health consequences; and (3) other devices that FDA has designated as requiring tracking. Under section 519(e), FDA believes that your device is a device that is subject to tracking because it is a permanent implant whose failure would be reasonably likely to have serious adverse consequences.

FDA's tracking regulations, published in the FEDERAL REGISTER on August 16, 1993, appear at 21 CFR Part 821. These regulations set out what you must do to track a device. In addition, the regulations list example permanent implant and life sustaining or life supporting devices that FDA believes must be tracked at 21 CFR § 821.20(b) and the devices that FDA has designated for tracking at 21 CFR § 821.20(c). FDA's rationale for identifying these devices is set out in the FEDERAL REGISTER (57 FR 10705-10709 (March 27, 1991), 57 FR 22973-22975 (May 29, 1992), and 58 FR 43451-43455 (August 16, 1993)).

If you have questions concerning this approval order, please contact Mitchell J. Shein at (301) 443-8517.

Sincerely yours,

Susan Alpert, Ph.D., M.D.
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosures

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Issued: 5-2-95

CONDITIONS OF APPROVAL

APPROVED LABELING. As soon as possible, and before commercial distribution of your device, submit three copies of an amendment to this PMA submission with copies of all approved labeling in final printed form to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration (FDA), 9200 Corporate Blvd., Rockville, Maryland 20850.

ADVERTISEMENT. No advertisement or other descriptive printed material issued by the applicant or private label distributor with respect to this device shall recommend or imply that the device may be used for any use that is not included in the FDA approved labeling for the device. If the FDA approval order has restricted the sale, distribution and use of the device to prescription use in accordance with 21 CFR 801.109 and specified that this restriction is being imposed in accordance with the provisions of section 520(e) of the act under the authority of section 515(d)(1)(B)(ii) of the act, all advertisements and other descriptive printed material issued by the applicant or distributor with respect to the device shall include a brief statement of the intended uses of the device and relevant warnings, precautions, side effects and contraindications.

PREMARKET APPROVAL APPLICATION (PMA) SUPPLEMENT. Before making any change affecting the safety or effectiveness of the device, submit a PMA supplement for review and approval by FDA unless the change is of a type for which a "Special PMA Supplement-Changes Being Effected" is permitted under 21 CFR 814.39(d) or an alternate submission is permitted in accordance with 21 CFR 814.39(e). A PMA supplement or alternate submission shall comply with applicable requirements under 21 CFR 814.39 of the final rule for Premarket Approval of Medical Devices.

All situations which require a PMA supplement cannot be briefly summarized, please consult the PMA regulation for further guidance. The guidance provided below is only for several key instances.

A PMA supplement must be submitted when unanticipated adverse effects, increases in the incidence of anticipated adverse effects, or device failures necessitate a labeling, manufacturing, or device modification.

A PMA supplement must be submitted if the device is to be modified and the modified device should be subjected to animal or laboratory or clinical testing designed to determine if the modified device remains safe and effective.

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A "Special PMA Supplement - Changes Being Effected" is limited to the labeling, quality control and manufacturing process changes specified under 21 CFR 814.39(d)(2). It allows for the **addition** of, but **not the replacement** of previously approved, quality control specifications and test methods. These changes may be implemented before FDA approval upon acknowledgment by FDA that the submission is being processed as a "Special PMA Supplement - Changes Being Effected." This acknowledgment is in addition to that issued by the PMA Document Mail Center for all PMA supplements submitted. **This procedure is not applicable to changes in device design, composition, specifications, circuitry, software or energy source.**

Alternate submissions permitted under 21 CFR 814.39(e) apply to changes that otherwise require approval of a PMA supplement before implementation of the change and include the use of a 30-day PMA supplement or annual postapproval report. FDA must have previously indicated in an advisory opinion to the affected industry or in correspondence with the applicant that the alternate submission is permitted for the change. Before such can occur, FDA and the PMA applicant**(s)** involved must agree upon any needed testing protocol, test results, reporting format, information to be reported, and the alternate submission to be used.

POSTAPPROVAL REPORTS. Continued approval of this PMA is contingent upon the submission of postapproval reports required under 21 CFR 814.84 at intervals of 1 year from the date of approval of the original PMA. Postapproval reports for supplements approved under the original PMA, if applicable, are to be included in the next and subsequent annual reports for the original PMA unless specified otherwise in the approval order for the PMA supplement. Two copies identified as "Annual Report" and bearing the applicable PMA reference number are to be submitted to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850. The postapproval report shall indicate the beginning and ending date of the period covered by the report and shall include the following information required by 21 CFR 814.84:

(1) Identification of changes described in 21 CFR 814.39(a) and changes required to be reported to FDA under 21 CFR 814.39(b).

(2) Bibliography and summary of the following information not previously submitted as part of the PMA and that is known to or reasonably should be known to the applicant:

(a) unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices ("related" devices include devices which are the same or substantially similar to the applicant's device); and

(b) reports in the scientific literature concerning the device.

If, after reviewing the bibliography and summary, FDA concludes that agency review of one or more of the above reports is required, the applicant shall submit two copies of each identified report when so notified by FDA.

ADVERSE REACTION AND DEVICE DEFECT REPORTING. As provided by 21 CFR 814.82(a)(9), FDA has determined that in order to provide continued reasonable assurance of the safety and effectiveness of the device, the applicant shall submit 3 copies of a written report identified, as applicable, as an "Adverse Reaction Report" or "Device Defect Report" to the PMA Document Mail Center (HFZ-401), Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, Maryland 20850 within 10 days after the applicant receives or has knowledge of information concerning:

(1) A mixup of the device or its labeling with another article.

(2) Any adverse reaction, side effect, injury, toxicity, or sensitivity reaction that is attributable to the device and

(a) has not been addressed by the device's labeling or

(b) has been addressed by the device's labeling, but is occurring with unexpected severity or frequency.

(3) Any significant chemical, physical or other change or deterioration in the device or any failure of the device to meet the specifications established in the approved PMA that could not cause or contribute to death or serious injury but are not correctable by adjustments or other maintenance procedures described in the approved labeling. The report shall include a discussion of the applicant's assessment of the change, deterioration or failure and any proposed or implemented corrective action by the applicant. When such events are correctable by adjustments or other maintenance procedures described in the approved labeling, all such events known to the applicant shall be included in the Annual Report described under "Postapproval Reports" above unless specified otherwise in the conditions of approval to this PMA. This postapproval report shall appropriately categorize these events and include the number of reported and otherwise known instances of each category during the reporting period. Additional information regarding the events discussed above shall be submitted by the applicant when determined by FDA to be necessary to provide continued reasonable assurance of the safety and effectiveness of the device for its intended use.

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REPORTING UNDER THE MEDICAL DEVICE REPORTING (MDR) REGULATION. The Medical Device Reporting (MDR) Regulation became effective on December 13, 1984, and requires that all manufacturers and importers of medical devices, including in vitro diagnostic devices, report to FDA whenever they receive or otherwise became aware of information that reasonably suggests that one of its marketed devices

(1) may have caused or contributed to a death or serious injury or

(2) has malfunctioned and that the device or any other device marketed by the manufacturer or importer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

The same events subject to reporting under the MDR Regulation may also be subject to the above "Adverse Reaction and Device Defect Reporting" requirements in the "Conditions of Approval" for this PMA. FDA has determined that such duplicative reporting is unnecessary. Whenever an event involving a device is subject to reporting under both the MDR Regulation and the "Conditions of Approval" for this PMA, you shall submit the appropriate reports required by the MDR Regulation and identified with the PMA reference number to the following office:

Division of Surveillance Systems (HFZ-531)
Center for Devices and Radiological Health
Food and Drug Administration
1350 Piccard Drive, Room 240
Rockville, Maryland 20850
Telephone (301) 594-2735

Events included in periodic reports to the PMA that have also been reported under the MDR Regulation must be so identified in the periodic report to the PMA to prevent duplicative entry into FDA information systems.

Copies of the MDR Regulation and an FDA publication entitled, "An Overview of the Medical Device Reporting Regulation," are available by written request to the address below or by telephoning 1-800-638-2041.

Division of Small Manufacturers Assistance (HFZ-220)
Center for Devices and Radiological Health
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

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Summary of Safety and Effectiveness

Medtronic Legend Plus®

Pacing System (P930022)

Table of Contents

Summary of Safety and Effectiveness

I. General Information

Device Generic Name:	Single Chamber Adaptive Rate Pulse Generator
Device Trade Name:	Legend Plus® Model 8446 and 8448 Pulse Generators Model 9790 and 9790C Programmers with the Models 9891 and 9807 Software
Applicant's Name and Address:	Medtronic , Inc. 7000 Central Avenue, N.E. Minneapolis, MN 55432
PMA Number:	P930022
Date of Notice of Approval to Applicant:	FEB - 7 1997

II. Indications

Legend Plus® pacemakers are intended for permanent ventricular or atrial pacing applications. Their use is indicated in the treatment of patients who may benefit from a pacing rate that changes in response to activity.

Ventricular indications include:

- chronic atrial flutter or fibrillation with slow ventricular response
- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, chronotropic insufficiency, etc.,)
- AV block

Atrial indications include:

- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, etc.,) with intact AV conduction.

NOTE: Data from the clinical trial do not establish an incremental benefit of the dual sensor mode over that achieved by the activity sensor mode alone, although the dual sensor mode appears to provide, for treadmill and bicycle exercise, a rate response which more closely mimics normal physiology (see "Clinical Studies" section below)

III. Contraindications

Atrial pacing is contraindicated in the presence of AV conduction disturbances (i.e., pre-existing AV conduction delay or block).

The use of Legend Plus® pacemaker for minute ventilation (MV) applications in abdominal placements is contraindicated because MV cannot be accurately measured.

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The implantation of the Legend Plus® pacemaker is contraindicated with an implantable defibrillator. The defibrillator may detect the current pulses that are emitted by the minute ventillation sensor and cause the defibrillator to withhold appropriate therapy or induce inappropriate therapy.

The use of epicardial leads with the Legend Plus® pacemaker is contraindicated because the measurement of minute ventillation with epicardial leads has not been demonstrated.

IV. Warnings

Rate Responsive Modes

Minute Ventilation (MV) rate response pacing may be inappropriate for patients who can achieve respiratory cycles shorter than 1.25 seconds (greater than 48 breaths per minute). In the event that faster respiratory rates occur the MV sensor-indicated rate gradually diminishes along a 2.5 minute deceleration curve toward the lower rate. For example, a respiratory rate of 60 breaths per minute will result in a sensor rate decrease to 30% of the maximum rate increase.

The programming of a rate responsive mode is not properly accepted by the pacemaker in about 1 out of 1200 mode programmings. The occurrence of this anomaly can produce unexpected variability in the pacing rate, including periodic beats as high as 185 ppm. This situation can occur only when the pacemaker is programmed (or reprogrammed) to a rate responsive mode.

A mode verification test is available to confirm whether or not the programming of a rate responsive mode occurred correctly and is automatically initiated upon programming a rate responsive mode.

Mechanical Ventilation

The Legend Plus® pacemaker may respond to changes induced by mechanical ventilation. To prevent pacing rate changes due to mechanical ventilation, program the pacemaker to a non-MV mode.

Minute Ventilation Lead Requirement

Minute ventilation requires the implantation of a transvenous bipolar lead. The Minute Ventilation rate responsive feature is inoperable when a unipolar lead is used.

An implanted lead with measured impedance greater than 1000 Ohms may result in attenuated Minute Ventilation rate response. When lead impedance is above 3000 ohms, Minute Ventilation rate response will not function.

Using Unipolar Leads

The Legend Plus® Models 8446 and 8448 can be connected to unipolar leads, however, programming the device to bipolar pacing with a unipolar lead results in an open circuit and the inability to obtain capture.

Asynchronous Pacing Modes

Asynchronous pacing (VOO/AOO or VOOR/AOOR) may be proarrhythmic in the presence of competition between paced and intrinsic rhythms.

High Rate Pacing

High rate stimulation of the ventricle may cause ventricular tachycardia or fibrillation. Application of high rate pacing should be performed only under careful patient monitoring, control, and with defibrillation equipment available. Temporary high rate pacing overrides the rate limit feature, however, it is not available in rate responsive modes.

Electromagnetic Interference

Certain types of electromagnetic interference (EMI) e.g., defibrillation, diathermy, and electrocautery, may damage the pacemaker and/or interfere with its operation, possibly leaving the patient without pacing therapy.

Electrocautery

Electrocautery units should never be used when replacing a Legend Plus® pacemaker. Currents generated from such units may cause a permanent loss of output.

Magnetic Resonance Imaging

The use of Magnetic Resonance Imaging (MRI) among pacemaker patients has been contraindicated by MRI manufacturers. Medtronic recommends against subjecting pacemakers patients to MRI scanning. Clinicians should carefully weigh the decision to use MRI with pacemaker patients. The following information is provided to the clinician to assist in careful consideration of the risks and benefits of subjecting pacemaker patients to MRI scanning, should the clinical circumstances arise. Limited studies of the effects of MRI on pacemakers have shown that:

- Magnetic and radio frequency (RF) fields produced by MRI may adversely affect the operation of the pacemaker and may inhibit pacing output.
- Magnetic fields may activate magnet mode operation and cause asynchronous pacing.

Reported[1] effects of MRI on pacing include increased ventricular pacing beyond the rate limit. Pacemaker patients subjected to MRI should be closely monitored and programmed parameters should be verified upon cessation of MRI.

Magnet Usage

Positioning a magnet or the programming head over the pacemaker converts it to asynchronous operation and makes it receptive to programming. Do not use electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pacemaker as inadvertent programming may result.

V. Precautions

Pacing Rates for Diagnostic/Pediatric Uses

Carefully monitor the patient when using pacing rates less than 40 or greater than 100 ppm in the demand mode. Rates less than 40 ppm are intended primarily for diagnostic purposes. Programmed rates of 120 to 130 ppm in the inhibited mode are intended for pediatric applications only.

NOTE: Lower Rates in the rate responsive modes are 40, 50, 60, 70, 80 and, 90 ppm. The physician should consider the rate requirements of a pediatric patient when considering the use of the rate responsive modes. With some very young children, the physician may elect to use the VVI/AAI mode to achieve higher pacing rates; then as the child becomes older, program the device to a rate responsive mode at a lower base rate.

[1] Holmes, Hayes, Gray, et al: The effects of magnetic resonance imaging in implantable pulse generators. Pace 1986; 9(3): 360-70.

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Premature Elective Replacement Conditions

Continuous pacing at high rates (> 100 ppm) and at wide pulse widths (up to 1.5 ms) in the demand, or rate responsive modes over a period of several years may cause the battery to indicate elective replacement time. If the battery voltage should temporarily fall to or below 2.5 V, the pacemaker paces at a 10% decrease from the programmed rate in the non-rate responsive mode and at 65 ppm in the rate responsive modes, both without a magnet. While operating at this rate, the battery may gradually recover. If the battery voltage rises above 2.5 V, the pacemaker may be reprogrammed following the battery reset command.

Sterile Package Damage

Inspect the pacemaker sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

MV Sensor Initialization

The MV Sensor should never be initialized prior to implantation.

The Rate Response Assistant Initialization Protocol should never be started when the device is connected to the Model 5311B Pacing System Analyzer (PSA). The PSA may cause the protocol's impedance interlock to inappropriately allow initialization of the MV Sensor at a pre-implant state.

The MV Sensor should only be turned ON once the pacemaker is placed securely in the closed subcutaneous pocket. If an acute lead requires repositioning, program the MV Sensor OFF prior to repositioning the lead.

Rate Increase Caused by "Twiddler's Syndrome"

"Twiddler's syndrome," i.e., patient manipulation of the device after implant, may cause the pacing rate to increase temporarily, if the device is programmed to a rate responsive mode.

Effects of Pressure in the Activity Mode

Clinical studies on the rate responsive, activity-detecting pacemakers have reported instances of increased sensitivity of the pacemaker to muscle motion (such as heart contractions) when external pressure is exerted on the device. Tests reveal a gradual increase in the pacing rate, but not up to the programmed Upper Activity Rate at nominal settings (Activity Threshold = Medium, Activity Rate Response = 7, Lower Rate = 60 ppm, Upper Activity Rate = 120 ppm). This might occur when the patient is lying on the pacemaker while sleeping, or by pressing the programmer head to activate the "Cancel Magnet" function over the pacemaker with the patient supine. Implantation of the pacemaker near the patient's skeletal system (e.g., in a very thin patient), may augment the effect when pressure is applied. This phenomenon does not indicate device malfunction or inappropriate programming. Relief of pressure on the implanted device should result in the pacing rate returning to the appropriate rate. Reprogramming the Activity Threshold to a higher setting reduces the effects of pressure and the potential for a rate increase.

Muscle Stimulation in the Activity Mode

Under certain circumstances (e.g., high output settings, a break in the device's insulative coating, etc.), the pacemaker can induce muscle stimulation at the pocket site. If this occurs with the Legend Plus® Models 8446 or 8448 in the unipolar polarity (when programmed to an Activity mode), the muscle contractions may be detected by the Activity sensor. Such detection, in turn, may result in a rise in pacing rate. The extent of rate elevation is dependent on the programmed Activity Rate Response setting, i.e., the higher the setting, the higher the pacing rate.

In such cases and at nominal settings (Activity Threshold = Medium, Rate Response = 7, Lower Rate = 60 ppm, Upper Rate = 120 ppm), the pacing rate remains below 110 ppm in a resting patient.

NOTE: Higher rates may occur at other settings such as Activity Threshold = Medium, Activity Rate Response = 10, Lower Rate = 90 ppm, Upper Activity Rate = 170 ppm. Upon termination of pacer-induced muscle stimulation, the pacing rate returns to its Lower Rate or to that level which corresponds to the activity being detected (i.e., nonpacer-induced). In most circumstances, muscle stimulation may be effectively controlled and/or alleviated by reducing the programmed amplitude or pulse width.

Effects of Electromagnetic Interference

The Legend Plus® pacemaker is immune to sensing common sources of electromagnetic interference (EMI). Various EMI sources exist or could become common in the future. The following paragraphs contain information on typical EMI sources within the hospital, medical, home, and job environments.

NOTE: In the presence of EMI, the pacemaker may become inhibited, pace to the Upper MV Rate in MV rate responsive modes, or revert to asynchronous pacing. Turn off the EMI source or move away from the source to return the pacemaker to its normal operation. Some types of EMI may reset the programmed settings.

Hospital and Medical Environment

Defibrillation

The pacemaker may be damaged by defibrillatory charges, possibly causing loss of pacing. In addition, defibrillatory discharges may result in temporary and/or permanent myocardial damage at the electrode-tissue interface, or temporary and/or permanent elevated pacing thresholds.

To reduce the risk of damaging the device, place defibrillation paddles at least 12 cm (5 inches) from the pacemaker and confirm pacemaker function following defibrillation. Defibrillatory charges may cause an electrical reset of the device or set the elective replacement indicators.

Diathermy

Therapeutic diathermy should not be used directly over a pacemaker since internal components may be damaged by heating.

Electrocautery

The electrocautery tip should never be used in the vicinity of [15 cm (6 inches) or closer] an implanted Legend Plus® pacemaker/lead system.

The use of electrocautery:

- can induce ventricular fibrillation,
- may cause permanent loss of output in either electrode configuration,
- may cause the pacing rate to rise to the Upper MV or Upper Activity Rate limit,
- may inhibit pacing output or revert the pacemaker to asynchronous operation, and
- may cause the pacemaker to go to electrical reset or elective replacement conditions.

The required level for such effects varies with the type of electrocautery unit, coagulation and cutting current settings, current pathway from the cautery tip to indifferent plate, and pacemaker/lead system.

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Because of all these potential complications, an alternative to electrocautery should be used, where available. Care must be taken to minimize the potential for any of the conditions described above when using electrocautery.

If using electrocautery is necessary, it is recommended that:

1. The device be programmed to the asynchronous mode (VOO/AOO).
2. The current path form the cautery electrode tip to indifferent plate should be kept as far away from the pacemaker/lead system as possible (e.g., the ground plate be located under the patient's buttocks or legs during abdominal surgery).
3. Short, intermittent, and irregular bursts at the lowest feasible energy levels be used.
4. Where possible, a bipolar electrocautery unit be used.
5. Temporary pacing and defibrillation equipment be readily available.

NOTE: In addition to the concerns noted above regarding the effects of electrocautery on pacemakers, these units may also interfere with electrocardiographic monitoring equipment. Therefore, if electrocautery is to be used on pacemaker patients, cardiac activity should be followed by continuous palpation of the peripheral pulse or by monitoring of the peripheral arterial or intraventricular pressure.

External Monitoring Equipment

Electrical current applied across the patient's thorax by external monitoring equipment, such as a respiration rate monitor, may affect the pacing rate in minute ventilation (MV) rate responsive modes. The current may be detected by the pacemaker's MV sensor, which may result in the pacing rate increasing up to the programmed Upper MV Rate. If external monitoring equipment is used, program the pacemaker to a non-MV mode prior to turning the equipment on.

Irradiation

The pacemaker should not be directly irradiated by therapeutic levels of ionizing radiation (such as produced by cobalt machines or linear accelerators used for cancer treatment) because of the risk of permanent damage to the pacemaker circuitry. If such therapy is required in the vicinity of the pacemaker, the pacemaker should be shielded and its function confirmed following treatment.

Lithotripsy

Permanent damage to the pacemaker may occur if the pacemaker is at the focal point of the lithotripsy beam. Since this situation is easily avoided, lithotripsy may be used provided:

1. The pacemaker is programmed to the VVI/AAI or VOO/AOO mode prior to treatment.
2. The pacemaker is further than 5 cm (2 inches) away from the focal point of the lithotripsy beam.

X-Ray and Fluoroscopy

Controlled exposure to diagnostic X-ray and fluoroscopic radiation has not affected the Legend Plus® pacemaker.

Home or Job Environment

Based on laboratory tests of the Legend Plus® pacemaker, the device should not be affected by the normal operation of electrical equipment such as household appliances, electric machine shop tools, microwave ovens, spark-ignited internal combustion engines, low-powered radio frequency transmitting systems or low-powered microwave frequency transmitting systems. All such equipment should be kept in good repair and properly grounded to avoid the possibility of electrical shock or interference with the proper operation of the pacemaker.

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Some types of theft prevention equipment, such as those found at store entrances and exits, may temporarily inhibit the Legend Plus® pacemaker or cause it to revert to asynchronous operation. The pacemaker returns to normal operation when the patient moves away from such equipment.

Medtronic should be consulted when the pacemaker wearer will be in areas where contact with current carrying conductors is possible or near high-powered electromagnetic fields radiated by arc welding units, induction furnaces, induction stoves, resistance welders, radio, or microwave frequency transmitters, etc.

Cellular Phones

Recent studies have indicated there may be a potential interaction between cellular phones and pacemaker operation. Potential effects may be due to either the radio frequency signal or the magnet within the phone and could include inhibition or asynchronous pacing when the phone is in close proximity (within 6 inches or 15 cm) to the pacemaker.

Based on testing to date, effects resulting from an interaction between the cellular phone and the implanted pacemaker have been temporary. Simply moving the phone away from the implanted device will return it to its previous state of operation. Because of the great variety of cellular phones and the wide variance in patient physiology, an absolute recommendation to cover all patients cannot be made.

Patients having an implanted pacemaker who operate a cellular phone should:

- Maintain a minimum separation of 6 inches (15 cm) between a hand-held personal cellular phone and the implanted device. Portable and mobile cellular phones generally transmit at higher power levels compared to hand-held models. For phones transmitting above 3 watts, maintain a minimum separation of 12 inches (30 cm) between the antenna and the implanted device.
- Patients should hold the phone to the ear opposite the side of the implanted device. Patients should not carry the phone in a breast pocket or on a belt within 6 inches (15 cm) of the implanted device as some phones emit signals when they are turned ON but not in use (i.e., in the listen or standby mode). Store the phone in a location opposite the side of the implant.

VI. Adverse Events

Events Reported During the Clinical Study

The clinical investigation of the Legend Plus pulse generator involved 262 devices implanted in 262 patients for a total of 4106 cumulative device months of experience (mean = 15.7 months). Sixteen patients died during the course of the clinical study. None of the deaths were judged to be related to the device. Adverse events (AEs) including 2 complications and 89 observations were reported during the clinical investigation. Table 1 reports these data on a per patient and a per patient-month basis.

Table 1. Adverse Events

Type of AE	# of Patients (n=262)	% of Patients	# AEs	AE / Pt-Mo (n=4106)	Pt. Mos Between AEs
Observations[1] (89)					
Inappropriate Programming	42	16.0%	51	0.0124	81
Hematoma/Seroma	8	3.05%	8	0.0019	513
Pacemaker Syndrome	5	1.91%	5	0.0012	821
Pain/Swelling at Pocket Site	4	1.53%	4	0.0010	1027
Failure to Capture	3	1.15%	3	0.0007	1369
Pacemaker Migration	2	0.76%	3	0.0007	1369
Angina	2	0.76%	2	0.0005	2053
Failure to Sense	2	0.76%	2	0.0005	2053
Inadequate Cardiac Output	2	0.76%	2	0.0005	2053
Inappropriate Rate Response	2	0.76%	2	0.0005	2053
Local Infection at Pocket	2	0.76%	2	0.0005	2053
Fatigue	1	0.38%	1	0.0002	4106
Fluttering at Pocket Site	1	0.38%	1	0.0002	4106
Systemic Infection	1	0.38%	1	0.0002	4106
Tachycardia	1	0.38%	1	0.0002	4106
Ventricular Oversensing	1	0.38%	1	0.0002	4106
Complications[2] (2)					
Inappropriate Device Operation	1	0.38%	1	0.0002	4106
Pacemaker Migration	1	0.38%	1	0.0002	4106

1 Observations are adverse events which are correctable by noninvasive measures, e.g., reprogramming.

2 Complications are adverse events requiring invasive measures to correct, e.g., surgical intervention.

Potential Events

Potential events not seen during the clinical trial, but commonly associated with cardiac pacing, include, but are not limited to, body rejection phenomena including local tissue reaction, fibrotic tissue formation, muscle and nerve stimulation, infection, erosion of pacemaker lead through skin, myopotential sensing, transvenous lead-related thrombosis, embolism, and cardiac tamponade. (See also "Potential Complications" in Table 2.)

Table 2. Potential Events

Component	Condition	Possible Event
Power Source	Premature depletion due to high internal losses	Output voltage decrease, no output, loss of capture, reversion to elective replacement parameters,* shortened time interval after elective replacement indicator is set.
Other Components	Electrical parameter changes due to shorts, open circuits or shifts in component parameters.	No output, rate change, reversion to asynchronous mode, loss of capture, loss of programming function, changes in parameter settings, reversion to elective replacement or electrical reset parameters.*
Circuitry	Electromagnetic interference (EMI) from power tools, equipment, appliances, etc.	Output inhibition, pace to the Upper MV Rate in MV modes, reversion to asynchronous mode, pacing synchronized to interference, reversion to reset parameters.*
	EMI from electrocautery	Permanent loss of output, output inhibition, reversion to asynchronous mode and rate change or instability, pace to the Upper MV Rate in MV modes, reversion to reset or elective replacement parameters.*
	EMI from defibrillator	Permanent loss of output, reversion to reset parameters.*
Connector	Poor Connection	Intermittent or continuous loss of capture, failure to sense properly.
Leads	Displacement or fracture	Intermittent or continuous loss of capture and/or sensing, inhibition of ventricular output.
		Minute ventilation detection ceases and lower rate pacing begins.
	Cardiac perforation	The above effects, plus cardiac tamponade, muscle or nerve stimulation.
	Myocardial irritability at time of insertion	Fibrillation, flutter.
	Pacing threshold elevation	Loss of Capture.
Activity Sensor	Open or short circuit	Activity detection ceases and lower rate pacing begins.
	Inappropriate detection, e.g., muscle stimulation, external mechanical stimulation, etc.	Rise in pacing rate, potentially to levels higher than expected or desirable
Minute Vent. Sensor	Open or short circuit	Minute ventilation detection ceases and lower rate pacing begins.
	Inappropriate detection, e.g., upper body motion.	Rise in pacing rate, potentially to levels higher than expected or desirable.

* See "Electrical Replacement Indicators" and "Electrical Reset Parameters" in the Appendixof the attached label for more information.

VII. Device Description

The Legend Plus® Models 8446 and 8448 are single chamber, lithium-iodine powered, implantable bradycardia pacemakers with rate variability based on either Activity or Minute Ventilation, or both. Use of standard transvenous bipolar leads is required for the use of the minute ventilation sensor. These pulse generators may be programmed with the Model 9790 and 9790C Programmers with the Models 9891 and 9807 Software.

The Legend Plus® pulse generator may be programmed to either unipolar or bipolar operation. The Model 8446 uses a low-profile (3.2 mm) lead or an IS-1 BI [ISO 5841-3:1992 Cardiac Pacemakers - Part 3: Low-Profile Connectors (IS-1) for Implantable Pacemakers] lead; the Model 8448 uses an IS-1 BI lead only. Both models may be connected to unipolar leads however Minute Ventilation rate response is available only when a bipolar lead is used.

In addition to providing demand, asynchronous or triggered pacing modes, the pacemakers can vary the pacing rate based on Activity, Minute Ventilation, or both Activity and Minute Ventilation. The activity sensor is a piezoelectric element contained within the pulse generator's titanium shield and the minute ventilation sensor measures transthoracic impedance.

Both pacemaker models are built using the same hybrid electronics. The connector is the only difference between the models. The Models 8446 and 8448 are configured by trimming a BICONN trim link.

The pulse generator is powered by a lithium-iodine battery (Promeon Sigma 303) with an open circuit voltage of 2.79 volts and a nominal deliverable capacity of 1.5 ampere-hours at an average current drain of 20 microamps.

The materials used in the Legend Plus® which contact body tissue consist of titanium (shields, connector blocks, set screws), polyurethane (connectors), silicone rubber (seals), silicone medical adhesive and parylene coating.

Pulse generator Models 8446 and 8448 can be programmed with the Model 9790 and 9790C Programmers with the Models 9891 and 9807 Software. The programmers use a firmware package that allows the clinician to reprogram or interrogate the pulse generator, request measured values, or cause it to telemeter continuous analog waveforms, or logged data values.

Several minor changes have been made to the Legend Plus® system from the version used in the clinical studies. These included

- Use of the Model 9790 and 9790C Programmers with the Models 9891 and 9807 Software.
- Removal of the Breathing Protocol
- Minor changes to the MV Initialization Protocol and the MV Exercise Protocol
- Setting of the MV Accel and MV Decel to fixed values of 0.5 and 2.5 respectively
- Changing of the Emergency value for Pulse Amplitude from 5 to 8 V
- Addition of an ECG filter to reduce artifacts from the 9760 programmer ECG display

SSIR Operation

SSIR operation in the Legend Plus® is the same as in any single chamber rate responsive pulse generator. When pacing in the SSIR mode, the pulse generator will pace the ventricle (atrium) asynchronously at the programmed lower rate or the derived activity sensor rate or the algorithm derived rate in an MV mode (in the case of dual sensor mode, whichever is greater) in the absence of sensed ventricular (atrial) electrical activity.

Additionally, the programming of a rate responsive mode is not properly accepted by the pacemaker in about 1 out of 1200 mode programmings. The occurrence of this anomaly can produce unexpected variability in the pacing rate, including periodic beats as high as 185 ppm. This situation can occur only when the pacemaker is programmed (or reprogrammed) to a rate responsive mode. mode verification test is available to confirm whether or not the programming of a rate responsive mode occurred correctly. See the programmer manual for instructions.

Sensor Operation: ACT

The activity sensor is a piezoelectric element contained on the pulse generator's nonetched side and is implanted so that it has intimate contact with muscle tissue. The sensor is deflected by mechanical activity. These deflections are converted by the ACT circuit into electrical signals which are "detected" only when they exceed the programmed activity threshold.

The programmed ACT Rate Response setting establishes the relationship of the pacing rate to the detected physical activity. The number of detected deflections per second, occurring above the programmed ACT Threshold, and the programmed ACT Rate Response setting determine the pacing rate. All ACT Rate Response curves are linear and extend from the programmed Lower Rate to the programmed Upper ACT Rate (see Figure 1). The Upper ACT Rate is the maximum rate which can be attained with any rate response setting.

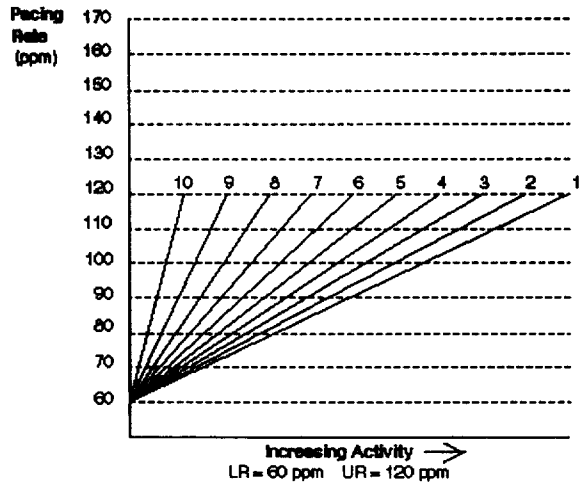

Figure 1 - Typical Linear Activity Rate Responses

ACT Threshold is the level (threshold) which must be exceeded before the resultant signals from sensor deflections due to activity are processed. The Low, Medium, and High settings are the same as in the Legend II; the additional intermediary ACT Threshold settings of Medium Low and Medium High are used to "fine tune" the ACT Threshold between the Low, Medium, and High settings.

The Activity Acceleration time is the time needed to achieve 90% of the sensor-indicated rate increase between a sustained lower activity level and a sustained higher activity level. Similarly, the ACT Deceleration time is the time needed to achieve 90% of a sensor-indicated rate decrease. The Legend Plus® provides the option of programming 1/4, 1/2, or 1 minute acceleration times and 2 1/2, 5, and 10 minute deceleration times.

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Sensor Operation: Minute Ventilation

When programmed to the MV rate responsive mode, the Legend Plus® pacemaker varies the pacing rate in response to changes in the patient's respiratory activity. The Legend Plus® pacemaker measures transthoracic impedance with a tripolar electrode using a standard bipolar lead and the pacemaker can. A biphasic stimulus of a 500 mA peak, 30 msec current pulse, with a sampling rate of 16 Hz is forced from the case to the ring. The resultant voltage referenced from the tip to the case is simultaneously sampled. The frequency of this sampled waveform correlates with respiration rate and the peak to peak amplitude correlates to tidal volume. Minute ventilation is the product of these two.

The actual derived pacing rate is dependent on the measured MV and the programmed values for Upper MV Rate, Lower Rate, MV Rate Response, and MV Range. The programmable MV Rate Response establishes the relationship of the pacing rate to amplitude and frequency changes in transthoracic impedance. The MV Rate Response parameter has 16 settings which are linear and start at the programmed Lower Rate (see Figure 2). The pacemaker can attain the Upper MV Rate in most programmed settings, and the MV sensor rate stabilizes and maintains a steady pacing rate between the Lower and Upper MV Rates when the sensed transthoracic impedance signal (amplitude and frequency) stabilizes. Minute Ventilation Range (MV Range) is a programmable parameter intended to limit the influence of transient, non-MV signals (e.g. arm motion), when measuring transthoracic impedance signals. Upper body motion can result in excessive impedance signals that could inappropriately cause higher MV sensor-indicated rates than the patient may require. The MV Range values (12.5, 25, 50 & 100%) are intended to limit the rate of change of the MV signal level; i.e., suppress large transient signals attributable to muscle "noise". For example, the "12.5%" setting limits the MV signal rate of change to 12.5% of the full-scale range (from lower to upper rate) during each two second interval, ignoring any excess signal. With sustained exercise MV signals or continuous muscle noise, the final rate achieved is independent of the programmed MV Range setting.

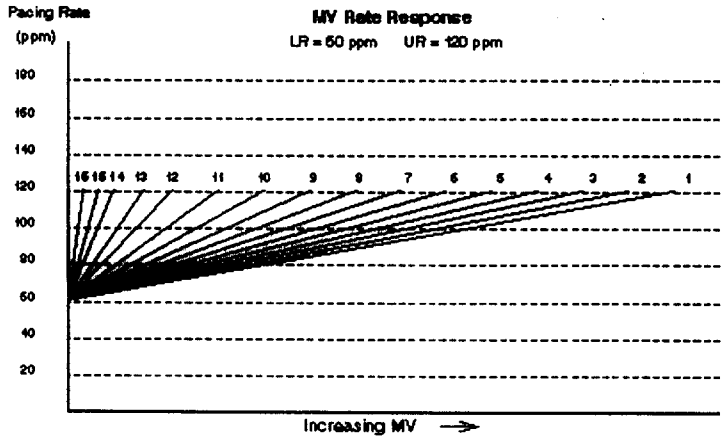

Figure 2 - Typical MV Rate Response Curves

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Dual Sensor Rate Responsive Mode Operation

The Legend Plus® pacemaker may be programmed to a Dual Sensor rate responsive mode which uses both ACT and MV sensors. As with the ACT mode, the pacemaker detects the patient's physical activity and varies the pacing rate in response to that activity. The pacemaker also varies the pacing rate according to amplitude and frequency changes in the patient's transthoracic impedance, which correlates to minute ventilation.

The ACT sensor is programmed in the same manner in the Dual Sensor mode as in the ACT mode. The ACT Threshold, ACT Acceleration and Deceleration Times, and the ACT Rate Response setting are determined by the physician as in the ACT alone mode.

The MV sensor is also programmed in the same manner in the Dual Sensor mode as in the MV mode. The MV Range and the MV Rate Response settings are determined by the physician as in the MV alone mode.

The programmed Lower Rate (escape interval) is the lower rate for both the MV and activity Sensors. Each sensor has separate programmable upper rates: the Upper ACT Rate for the ACT Sensor, and the Upper MV Rate for the MV sensor. The two upper rates are recommended to be programmed to different values (ppm). For example, a patient in the Dual Sensor mode may use an Upper ACT Rate of 110 for Moderate activity (e.g., walking), and an Upper MV Rate of 140 for extended exercise (e.g., bicycling). Each sensor-indicated rate is limited by its respective upper rate. The difference in Upper Rates can be used to segment the activity to allow the ACT sensor be predominate at lower workloads and the MV sensor at higher workloads.

In the Dual Sensor mode, each sensor determines separate pacing intervals. The pacing output is delivered based on the shorter pacing interval (higher pacing rate). The sensor interval time-out can vary between the two sensors on an interval-by-interval basis. As both sensor-indicated rates increase, the transition from one sensor-derived rate to the other may occur (see Figure 3).

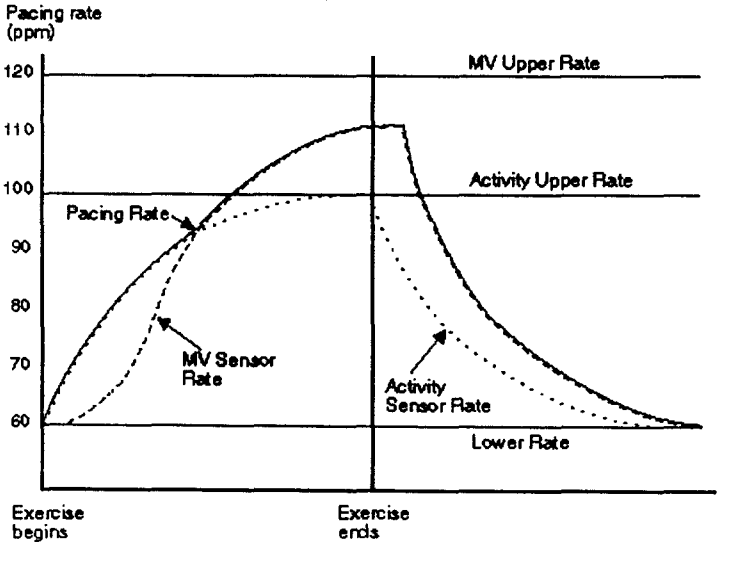

Figure 3 - Interaction of MV/ACT Sensors to Pacing Rate

Data from the clinical trial do not establish an incremental benefit of the DUAL sensor mode over that achieved by the ACT sensor mode alone, although the DUAL sensor mode appears to provide a rate response to exercise which more closely mimics normal physiology.

Minute Ventilation Protocols

Programming the Legend Plus® pacemaker to the Minute Ventilation (MV) pacing mode is accomplished using the protocols described below.

- Initialization Protocol: Used to turn the MV sensor ON and set the MV Gain setting; suggests nominal values for dual sensor operation.

- Exercise Protocol: Used to determine the recommended MV Rate Response and ACT Rate Response settings.

Once the MV Sensor is turned OFF, the Initialization Protocol is the only means to turn the MV Sensor back ON. The sequence of events performed during the Initialization Protocol are as follows:

- The programmer automatically tests lead impedance via Real-Time Telemetry. If the lead impedance exceeds 3000 Ohms, the programmer will not allow the protocol to proceed. The lead impedance test is intended as an interlock to prevent initialization of the MV Sensor prior to implant.

- The MV Sensor is turned ON and begins measuring the patient's transthoracic impedance.

- The protocol includes a 100 second countdown during which the programmer determines an appropriate MV Gain setting. The MV Gain setting is the impedance range that the patient's physiologic transthoracic impedance signal falls within.

Upon successful MV sensor initialization, the following nominal values for dual sensor operation are offered:

LR - 60ppm
ActUR - 100ppm
ActRR - 9
MVUR - 120ppm
MVRR - 4

The user has the option of either programming these values or proceeding to the Exercise Protocol to determine optimal values.

The Exercise Protocol recommends an MV Rate Response setting based on the patient's transthoracic impedance characteristics. The protocol includes a 2 minute countdown after which the programmer determines and displays recommended values for MV Rate Response and ACT Rate Response. The physician selects the Lower Rate, Upper MV Rate, and Upper ACT Rate that is appropriate for the patient. The physician also selects a target rate, which is the desired rate that the patient should ideally achieve for the chosen exercise.

During the countdown, transthoracic impedance values and activity driven paced events (recorded by Event Counters and displayed in Histograms) are collected during low/moderate level exercise. Based on the transthoracic impedance values and the pending Lower, Upper MV, and target rates, the programmer recommends the MV Rate Response setting.

The Exercise Protocol also may determine that another MV Gain setting would be more appropriate (based on MV data collected during the protocol), and give the user the option of reinitializing at the next higher or lower MV Gain setting (as appropriate).

The programmer also recommends an ACT Rate Response setting based on Event Counter (Histogram) heart rate data and the pending programmed Lower, Upper ACT and target rates.

Diagnostics

The diagnostic features in the Legend Plus® pulse generator are described in detail in the technical manual. Several options are available within the Event Counters feature.

Source is a programmed parameter that defines the event that will be used in the Event Counters. There are six selections: Heart Rate, Heart Rate plus Refractory, Sensed Rate, Sensed Rate plus Refractory, ACT Sensor Rate and MV Sensor Rate. ***Bins*** refers to the rate ranges in which events will be placed. Choosing the parameter Term defines the number of events that will be averaged into a single data point. Each of these averages is used in the system as one data point. Acute, short, medium, and long are choices that define the resolution obtainable. ***Format*** may be either histogram or trend (rolling or frozen).

Legend Plus® contains two high rate Event Counter capabilities: High Rate episodes (up to 15) are recorded whenever eight or more consecutive intrinsic events occur above a preset "trigger" rate. High Rate histogram mode is similar to the standard and expanded histogram modes, but uses higher-value bin ranges.

Real Time Telemetry

Upon request, the Legend Plus® pacemaker measures the battery voltage and output capacitor voltage change during the output pacing pulses. The measurements are digitally encoded and telemetered to the programmer. The programmer uses the telemetered information to calculate and display the following device operation information:

- Battery Voltage
- Lead Impedance
- Pulse Amplitude
- Output Energy
- Battery Current
- Lead Current
- Pulse Duration
- Battery Status

Electrogram (EGM)

The telemetry modes include an electrogram of the paced chamber. The intracardiac voltage signal on the pacing lead is pulse-interval encoded and uplinked to the programmer for decoding and display or print-out. The EGM may be monitored on the programmer screen or via an external ECG monitor in much the same way as the Marker Channel recording is monitored.

MV Electrogram

The Legend Plus® pacemaker telemeters the transthoracic impedance signal. A voltage representing the impedance is pulse-interval encoded and uplinked to the programmer for decoding and display or print-out. The MV Electrogram may be monitored on the programmer screen or via an external ECG monitor in much the same way as the Electrogram or Marker Channel recording is monitored.

Marker Channel

The operation of the Marker Channel in Legend Plus® is available through the programmer and allows determination of which sensor caused the paced cardiac event. Legend Plus® pacemakers have two telemetered Marker Channels, each of which may be printed. The two Marker Channels are the Pace/Sense marker and Pace Marker, and are available for rate responsive and non-rate responsive modes.

Programming

The programming mechanism utilized by the Legend Plus® pulse generators is performed with a Model 9790 or 9790C Programmer with the Models 9891 and 9807 Software. Programming the Legend Plus® pulse generators is accomplished by means of radio-frequency (RF) coupling between the programming head and the pulse generator.

Program Confirmation Indicator

To determine receipt and acceptance of a program transmission, the Legend Plus® pulse generator transmits telemetered data (i.e., the programmed parameters) for comparison by the programmer. If the parameters are the same as programmed, the programmer will indicate acceptance with a program confirmed message. To document a permanent change via ECG monitoring, the pulse generator emits a program confirmation indicator (PCI) which consists of a 10% rate increase for one pacing cycle.

Threshold Margin Test

The Threshold Margin Test (TMT) serves to indicate whether the output energy for the currently programmed pulse width provides sufficient reserve above the patient's stimulation threshold for safe pacing. After application of the magnet, there are three asynchronous pulses at 100 ppm (80 ppm below Elective Replacement Indicator voltage). The first two pulses are at the programmed pulse width; the third will show a 25% reduction in pulse width. This increase in magnet rate and reduction in pulse width will be canceled if programming occurs simultaneously

Auto Threshold

The auto threshold function is a programmer function which, when used in conjunction with electrodes and an ECG recorder, allows the physician to noninvasively measure the patient's pulse width stimulation threshold. The programmer automatically reduces pulse width in specified increments every six pacemaker output cycles. The shortest pulse width attained prior to loss of capture, as noted on the ECG, is the threshold pulse width

Battery Depletion Indicator

The operation of the Model 8446 and 8448 pulse generators change when the battery voltage falls below the Elective Replacement Indicator (ERI) threshold of 2.51V. Pulse generator operation also changes with the application of a magnet; this operation change depends on the mode to which the pulse generator has been programmed. In the Legend Plus® pulse generators, the Elective Replacement Indicator (ERI) is

- A change from SSIR to the demand (SSI) mode with a rate of 65 ppm (Rate Response mode only), or
- A 10% decrease in the programmed rate or 20% decrease in the magnet rate (non-Rate Response modes).

VIII. Alternative Practices and Procedures

While surgery or drug therapy may be alternatives to cardiac pacing in certain instances, cardiac pacing is often the standard treatment for the indications described in Section II above. Other commercially available single- or dual-chamber pulse generators provide alternatives to the Legend Plus ® Models 8446 and 8448 pulse generators.

IX. Marketing History

Over 3,700 Legend Plus® pulse generators have been commercially distributed outside the U.S. including Africa, Asia, Australia, Canada, Europe, Japan, Latin America, and the Middle East. Medtronic has notified users and responsible regulatory authorities regarding the potential for high rate pacing and how this issue has been addressed. The particulars regarding this issue are detailed in Section XIII - FDA Decision. Medtronic has not been informed of any devices that have been withdrawn from the market for reasons associated with the safety and/or effectiveness of the Legend Plus® pulse generators.

X. Summary of Studies

A. Nonclinical Studies

The following section provides a summary of the laboratory testing which was performed on the Legend Plus® pulse generators to evaluate safety, reliability and performance. (Animal testing was not required for the Legend Plus® pulse generator since 1) the device is physically and functionally similar to the Medtronic Legend and Legend II devices which were the subjects of approved Premarket Approval applications and 2) the canine model was deemed inappropriate for Minute Ventilation correlation to workload when measured using the Legend Plus® pulse generator.)

Hybrid Electronic Module Testing

Electrical and mechanical qualification activities were performed on a sample of 76 electronic modules. Each module was electrically stressed to 1000 hours of operating life test at 3.3 volts and 125°C. All units were tested before and after stress using a computer test system which simulates the performance of the pacing system and environment.

There was one unit that failed analog telemetry at the 500 hour test. Analysis suggested the failure was due to either an integrated circuit (IC) threshold shift or a resistor value change; further cause could not be identified and the unit was considered to be a random qualification failure. All other units completed the 1000 hour life test successfully. Following the life test, five units were analyzed for wire and die adhesion strength, and five for moisture content. All units met all specifications.

Integrated Circuit Testing

The Legend Plus® pulse generator contains three integrated circuits, a Pacing/Sensing Controller IC, an ACT/Event Counter IC and an MV Processing IC. To qualify the Pacing/Sensing and the MV Processing integrated circuits for the Legend Plus® pulse generator, a sample of 76 of each was assembled into pin-grid-array packaging for life testing. (The ACT/Event Counter IC had been qualified for the Legend II pulse generator and did not require repeat qualification for use in the Legend Plus®.) Electrical stability was qualified by placing the samples on life test at 4.2 V and either 150°C for 184 hours (Pacing/Sensing IC) or 125°C for 1000 hours (MV Processing IC). All units were tested before and after life test on a computer test system designed for both high speed logic testing as well as analog signal processing capabilities. There was one electrical failure for the Pacing/Sensing Controller IC; however the cause was identified and no corrective action was necessary. There was also one failure for catastrophic current drain in the MV Processing IC qualification; the cause was also identified and no corrective action was required. All remaining ICs completed the life test successfully.

Battery Testing

The power source used in the Legend Plus® pulse generators is a 2.8 V, 1.8 Ah cell. The battery was subjected to accelerated discharge, application discharge and environmental tests. Sixty-two samples were discharged at accelerated rates of 400, 200 and 100 micro Amps at 37°C. The average capacity delivered to the 2.5 V cutoff at 20 micro Amps was 1.67 Ah. All accelerated test samples performed reliably and met the design capacity ratings. Twelve cells on application discharge at 26 micro Amps have delivered 1125 mAh and have been performing normally for 4 1/2 years. Sixteen batteries were successfully subjected to shock and vibration tests, low temperature storage and high temperature storage.

Connector Testing

Fluid leakage tests were conducted on twenty-two Model 8446 connectors paired with 3.2 mm low profile bipolar leads followed by 22 IS-1 bipolar leads, and 22 Model 8448 with IS-1 bipolar leads to determine the electrical leakage of the connector. Impedance between the ring/tip, the tip/electrode and the ring/electrode was determined. The immersion solution was 0.9% NaCl providing an electrical resistivity of 50 ohm-cm at 37°C; leakage impedance measurements were taken at 100 Hz daily for 10 days. All devices met the minimum requirements of 50 K ohms. The connectors were also subjected to IS-1 insertion force testing with a 0.106 inch pin gauge; all connectors met the IS-1 insertion force requirement of 9 Newtons (2 pounds). All connectors were subjected to go-gauge testing; all accepted the go-gauge. All forty-four connectors also met the Medtronic requirements for lead insertion (3 pounds maximum) and extraction (2.5 pounds maximum).

Biocompatibility Testing

The materials used in the Legend Plus® pulse generator which come into contact with bodily tissue, Titanium, MP35N, Pellethane Polyurethane 75D, Silicone Rubber and Parylene, have been used in Medtronic pulse generators for several years. They have been subjected to standard biocompatibility tests (intramuscular implant in rabbits, tissue culture, USP pyrogen, hemolysis, USP Class V biological tests and Ames salmonella/microsome test for mutagenicity) and were shown to be biocompatible and suitable for human use.

Environmental Testing

Environmental stress testing was conducted on twenty-two Legend Plus® Model 8446 pulse generators to ensure adequate performance in typical operating, shipping and handling environments. The tests consisted of storage at temperatures of -18°C and 55°C for a minimum of six hours; mechanical vibration (5 Hz to 500 Hz to 5 Hz at 2.5 g); and mechanical shock (750 g, 1 msec/effective free-fall height of 18 inches). The devices were checked with a Model 5311 Pacing System Analyzer to evaluate device performance. All samples met all performance requirements. Reed switch closure and uplink and downlink telemetry field patterns were mapped using the 9760 Programmer; the Legend Plus® coincident telemetry area is slightly larger, and therefore acceptable, when compared to comparably sized Medtronic pulse generators. Six Legend Plus® devices were subjected to dynamic physical contact simulating pocket site muscle stimulation to ensure the pulse generator will not exceed the upper rate limit under intense physical activity. The ability of the Legend Plus® to maintain an increased rate without exceeding the programmed Upper Rate or the device Rate Limit was verified.

Electromagnetic Compatibility (EMC) Testing

EMC testing of the Legend Plus® pulse generators was accomplished to determine performance under the influence of various electromagnetic interference conditions. Standard testing formats were utilized to simulate actual and potential environmental situations. The possibility of interference causing inappropriate programming of device parameters was also evaluated. Sixty-four Model 8446 devices with beginning of life (BOL) and depleted batteries were subjected to

- modulated and continuous wave 450 MHz radiated electric fields,
- conducted sine wave interference at frequencies of 50, 60 and 400 Hz
- characterization testing at 3.5, 28.5 and 2450 MHz, and
- cautery and defibrillation testing

During each test pulse rate, pulse amplitude and pulse duration were monitored for any change due to the testing performed. The devices passed the requirements for radiated electromagnetic fields up to a level of 350 V/M RMS, and were not significantly affected by conducted sine interference. No interference-related programming occurred with continuous or pulsed signals up to the levels tested.

Thirty-two in vitro samples were subjected to a range of output levels (minimum to maximum) of electrocuatery currents for sine cutting, spark cutting and spark coagulation settings. All samples were also subjected to three 400 J (320 J delivered) defibrillation pulses in each paddle polarity. All devices met specification requirements; devices returned within the allowed time to programmed parameter values; those that reverted to power-on-reset (POR) conditions were able to be reprogrammed.

Testing of the Legend Plus® in regard to cellular telephones consisted of in vitro simulation testing, and exposure to actual analog and digital telephones. No anomalies or issues were observed as a result of exposure to the call-in/call-out functions of the analog and digital telephones used to perform the testing. In vitro simulation testing was performed at the three frequencies, 836, 900 and 950 MHz, which represent the mid-range frequencies of subscriber transmitters for systems in North America, Europe and Japan, respectively. The results show no effect on the Legend Plus® device up to the maximum equipment output of 400 V/m rms.

Minute Ventilation Testing

The Minute Ventilation (MV) rate response design was tested at the hybrid level to verify the proportional relationship between increases in the MV impedance signal and increases in the pacing rate. The testing verified the increase in rate that results from proportional increase in the product of frequency and amplitude of the input impedance signal. Design testing of the MV Range verified the limiting effect MV Range had on the rate response to a large transient impedance signal. The MV Initialization Protocol was tested to ensure the 9760 Programmer locks out initialization at impedance values greater than 3000 ohms, and to ensure reed switch closure did not affect the initialization protocol after the initialization procedure had begun. Both were verified. The MV Exercise Protocol was tested to ensure the protocol gives a MV value that increases with increasing impedance signal, and to characterize the appropriateness of the resulting rate. The procedure verified that, in all cases, an increasing impedance signal led to an increased value of MAXMV, and the MAXMV value was monotonically increasing over the course of the exercise protocol.

Parameter Stability Testing

Testing was performed on Legend Plus® pulse generators to determine the stability of device pacing parameters when subjected to varying environmental conditions. Rate, Pulse Width, Amplitude and Sensitivity were evaluated vs. Temperature (20°C-45°C), Load Resistance (100-2000 ohms) and Battery Voltage (50%-105% of Nominal). All of the parameters tested remained stable under the varying test conditions.

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Event Counter Testing

The Event Counters in the Legend Plus® pulse generator perform a diagnostic function in aiding the physician to evaluate the performance of the pacing system. The Event Counters collect data as paced and sensed events and display the data via Trend Analysis, Histogram or High Rate Episodes formats. The Event Counters in the Legend Plus® were evaluated on the bench under a variety of scenarios to verify function. The expected results for each scenario were determined. In all cases, including all four Event Counter parameters (Format, Term, Bins, Source) the actual results were the same as the expected results. The Event Counter function in the Legend Plus® pulse generator performed as designed.

Pulse Generator Predicted Reliability

Failure rate predictions and reliability goals for the Legend Plus® were established through traditional methods. At the 90% confidence level, the projected device average failure rate will be less than 0.024% per month, and at the 50% level, less than 0.015% per month. Based on these projections, the projected reliability at six years will be greater than 98.3% and at 8 years, greater than 97.7% at a 90% confidence level (best estimate).

Failure Modes and Effects Analysis (FMEA)

Failure Modes and Effects Analysis (FMEA) tests were performed on a Legend Plus® breadboard. Several failure mechanisms were induced in several of the Legend Plus® operating parameters. There was one condition which caused the device to exceed the rate limit; analysis of the failure indicated the condition would not be present on product that is shipped, and the design was determined acceptable for implant. Other failures included no output condition on the ventricular channel, increase of current drain above 100 micro Amps, failure to respond to programming, and lack of atrial or ventricular sensing. These results were as expected.

System Testing

The Legend Plus® pulse generator Models 8446 and 8448 are designed to be programmed and interrogated with the Medtronic Models 9790 and 9760 Programmers with the Model 9870E Software, and with the Model 9710A Programmer with the 9749 Memory Mod.™ System testing evaluated the use of the pulse generator with the programmer, software, patient monitors and pacing system analyzers to assure their operation was within the limits of their respective specifications. The system testing of the Legend Plus® pulse generator and ancillary equipment demonstrated that all parts functioned acceptably.

Software Testing

The Models 9891 and 9807 Software were developed and tested in accordance with Medtronic's formal procedures for the development and testing of software modules. These procedures include development of a Software Requirements Specification, a detailed design specification, a Hazard Analysis, a Module test Plan, a retest strategy and a Verification Test Specification. The software was tested per the Verification Test Specification. Errors, anomalies and inconsistencies were noted in Engineering Report Forms and all corrections were made. Following the successful final retest of the software, a final configuration audit was performed by Software Quality Engineering to ensure that all documents and code were properly controlled and released which they had been.

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B. Clinical Studies

The Clinical data provided in support of this PMA were accrued under a common investigational plan approved under G920086. The report of this clinical trial has a cut-off date of February 20, 1995 and as of that date 262 devices had been implanted in 262 patients (141 US) accounting for 4106 documented "device-months" at 46 investigational centers (24 US). The mean implant duration is 16 months with a maximum of about 32 months.

The three most prevalent indications regarding cardiovascular history and gender were evaluated using a Chi-Square test or Fisher's Exact test. Age was analyzed using a t-test. Multiple testing was corrected using the Bonferroni procedure which maintains an overall p-value of 0.05 (0.05/no. tests). Of the 262 patients, 93 (36%) were females. Inclusion and exclusion criteria were chosen to avoid gender bias. The preponderance of male patients reflected both the gender referral pattern for cardiac disease and the severity of the disease in the centers involved. Separate analyses of safety and effectiveness data for both male and female patients indicated no differences between the genders; hence, the data presented on the following pages is representative for both men and women.

A comparison to the previous single chamber Legend device study showed no statistical difference in the gender distribution, see Table 3.

Table 3 Patient Gender - Legend Plus® vs. Legend

STUDY	Gender	N	Percent
LEGEND PLUS®	Male	169	64%
	Female	93	36%
LEGEND	Male	123	58%
	Female	88	42%

Chi-Square P-Value: 0.167

Since the indications for use of the device were not gender related and since the female population in both the intensive and general phases of the study were sizable (93 of 262 patients), there was no impact on the interpretation of the data generated.

The primary objectives of the investigation were to demonstrate the clinical safety, efficacy, and utility of the MV and DUAL sensor (MV+ACT) modes in patients requiring chronic pacing. Evaluation included a battery of exercise protocols and Holter monitoring sessions. Additionally, software features including the "Initialization", "Breathing", and "Exercise" protocols; the parameter "MV Range": and the electrogram and marker channel function were evaluated. The Breathing protocol was found not to be useful for recommending MV parameter values and was removed. However, the exercise protocol was found to provide a reasonable recommendation for "MV Rate Response". The "MV Range" parameter was found to be of limited use in reducing rate accelerations in response to upper body/arm movement, however, this parameter is to be maintained for specific patient use. Further, the clinical data suggested the need for only a single setting for the MV acceleration and deceleration parameters of 0.5 and 2.5 minutes respectively.

The results show that the rate adaptive modes of the Legend Plus® provided appropriate rate response. Extensive Holter monitoring has been performed including 94 tests in the MV mode, 106 in the ACT mode, and 133 in the DUAL mode. Response to an Investigator questionnaire showed that investigators believed that the Holters "demonstrated appropriate pacing and sensing in all three sensor modes." They also reported that "adequate rate response was achieved in 73, 83, and 85% of the time in the ACT, MV, and DUAL modes respectively."

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For 171 patients screened for chronotropic incompetence (CI), 123 (72%) met one of the three study definitions (116 by the inability to achieve a heart rate >100bpm, 7 via the Wilkoff technique, and none by the inability to achieve 60% of their age predicted maximum heart rate). Of these 123 CI patients 30 patients were able to complete bicycle testing and 60 were able to complete treadmill testing (see Table 4). Neither the bicycle nor the treadmill testing demonstrated differences between the three sensor modes for exercise duration. Of the 90 patients who completed exercise testing in all 3 modes; 58 had metabolic data collected during their exercise. Of these 58, only 40 (24 treadmill and 16 bicycle) were determined to have reached their anaerobic threshold. No statistically significant difference was seen in the time to anaerobic threshold or maximal exertion time.

Submaximal exertion oxygen kinetics testing to assess the efficiency of the patients oxygen consumption was also performed on 25 patients (16 treadmill and 9 bicycle). The treadmill testing showed a statistically significant reduction in: a) oxygen deficit, and b) mean response time in favor of the ACT and DUAL modes. The 9 patients performing testing on the bicycle did not demonstrate either.

Table 4. Clinical results based on selected chronotropically incompetent patients (mean ± s.d.)

Test	N	ACT	MV	DUAL	Difference
Treadmill Exercise Duration (min.)	60	13 ± 3	13 ± 3	13 ± 3	
Treadmill Time to Anaerobic Threshold (min.)	24	11 ± 3	11 ± 3	11 ± 3	
Treadmill Percent of Upper Rate*	60	85 ± 13	90 ± 14	93 ± 12	MV & DUAL > ACT[1]
Bicycle Exercise Duration (min.)	30	9 ± 3	9 ± 3	9 ± 3	
Bicycle Time to Anaerobic Threshold (min.)	16	7 ± 3	7 ± 2	7 ± 2	
Bicycle Percent of Upper Rate*	30	72 ± 14	88 ± 16	89 ± 15	MV & DUAL > ACT[1]
Treadmill O_2 Deficit (ml/min.)	16	663 ± 315	912 ± 421	656 ± 251	ACT & DUAL > MV[2]
Treadmill Mean Response Time (sec.)	16	56 ± 15	73 ± 21	57 ± 21	ACT & DUAL > MV[3]
Treadmill Heart Rate 1st Minute (ppm)	48	27 ± 15	16 ± 17	26 ± 14	ACT & DUAL > MV[1]

* Note absence of correlation to measured physiologic benefit

[1] Difference by paired comparison (Repeated Measures Analysis of Variance) p = 0.0001

[2] Difference by paired comparison (Repeated Measures Analysis of Variance) p = 0.0254

[3] Difference by paired comparison (Repeated Measures Analysis of Variance) p = 0.0029

Additionally, testing was performed for "Activities of Daily Life" (ADL), i.e. activities which are to be representative of those which patients might partake in as part of their daily routine. Twenty-three patients who were identified as chronotropically incompetent at the 2 week screening completed all 3 randomized modes of the ADL testing. This testing showed that in those activities including significant upper body movement (showering, vacuuming, and "chores") a statistically significant increase in maximum heart rate (for showering and chores) and percent heart rate reserve (for vacuuming and chores) resulted.

One unanticipated adverse device experience was reported during the course of the clinical trial. Specifically a patient presented with an unexpected high rate which was determined to be due to the device being driven by both the MV and ACT sensors simultaneously. On analysis, this event was attributed to a random component failure and the patient was reprogrammed to the ACT mode without removal of the pacemaker or subsequent problems.

Clinical events were reported as "protocol deviation", "device related event", and "non-device related event." Device related events were defined as a symptomatic or asymptomatic clinical event which is a direct result of the patient having a pacing system. Non-device related events were defined as a symptomatic or asymptomatic clinical event which is unrelated to the patient's having a pacing system. "Device related" events were further subclassified as "complications" or "observations". "Complications" were defined as an event requiring invasive intervention; whereas an "observation" was defined as an event which is resolved by non-invasive means, e.g., reprogramming.

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Two protocol violations were reported involving a single investigator's use of an unapproved software version in the follow-up of 2 patients.

In addition to the high rate pacing incident reported above, two device related complications were reported and 89 device related observations. The complications reported included the unanticipated adverse device experience noted above and one case of pacemaker migration. The 89 "observations" were classified as follows: angina (2), failure to capture (3), failure to sense (2), fatigue (1), "fluttering at pocket site (1), hematoma/seroma (8), inadequate cardiac output (2), "inappropriate programming" (51), inappropriate rate response (2), local pocket infection (2), pacemaker migration (3, does not include above reported complication), pacemaker syndrome (5), pain/swelling at pocket site (4), systemic infection (1), tachycardia (1), and ventricular oversensing (1). All of the reported observations were resolved. Further, the "complications" experienced were "not statistically different in type or frequency from those associated with the Legend." In addition to the above noted device related events 243 "non-device related events were reported.

Sixteen patient deaths were reported. None of these deaths were judged to have been device related. The causes of death were noted to be: cardiorespiratory arrest, multiple system failure, congestive heart failure (2), cerebrovascular accident (2), acute lymphocytic leukemia, sudden cardiac death (2), myocardial infarction (3), heart failure, cerebral hemorrhage, hemorrhagic pancreatitis, and a tachyrhythmia.

Seven units were explanted, 4 for an "upgrade" to a dual chamber system, one for pocket infection/sepsis, one in favor of a tachyrhythmia device, and one additional unit was explanted due to infection with no further information reported.

Ten patient were lost to follow-up, 4 patients requested removal from the trial, 2 refused to return for follow-up, 3 patients were deemed lost due to non-compliance with the protocol, and 1 patient withdrew due to relocating.

One patient complaint addressing 2 issues was filed with the US Pharmacopia. The first issue dealt with "repeated problems with increased pulse rate with arm movement;" and the second that informed consent from the patient to participate in the trial was sought after the implantation of the device. Rate acceleration with upper body movement is consistent with the findings of the activities of daily living testing. Regarding the second issue, Medtronic noted that in follow-up with the investigator, the investigator noted that verbal consent had been obtained prior to surgery.

There has been one return for premature ERI (elective replacement indicator) after programming to the MV sensor mode. This device was analyzed and the event attributed to a failure within the MV processing IC. It is the only failure of this type that has been noted by Medtronic, and is considered random.

XI. Conclusions Drawn from the Studies

All three modes were evaluated (ACT, MV and DUAL), and performed safely and effectively. The benefit of single sensor rate response (ACT or MV) versus no rate response has been previously proven. The Legend Plus® study attempted to discern differences between three rate responsive modes. Combining the ACT and MV sensors into a third DUAL rate responsive mode provides a different heart rate profile than either of the single sensor modes alone. The O_2 kinetics testing during a constant workload test demonstrated that the two modes involving the ACT sensor (ACT and DUAL) provided a quicker chronotropic response and a lesser O_2 deficit at the onset of exercise than did the MV sensor alone ($p<0.002$). The difference in the percentage of the minimum programmed heart rate acheived during maximum treadmill and bicycle testing involving the MV sensor (MV and DUAL) is statistically significant ($p<0.001$); however, this does not correlate with a measured physiologic benefit. Time to anaerobic threshold and exercise duration time did not differ statistically among the three modes (ACT, MV, and DUAL).

Limitations of this study

Evaluation of the benefit of one rate response profile over another is limited by the available testing techniques. Evaluation of subtle differences in a patient's physiological state is difficult to do via non-invasive methods. Such evaluations are complicated by the extensive number of factors which contribute to the patient's general health and condition. The limitation of the Legend Plus® study is that while demonstrating a preferable rate profile in the DUAL mode during treadmill and bicycle exercise, it failed to provide a definitive answer to the question of whether the patients physiological state is better during any type of exercise.

XII. Panel Recommendations

The Circulatory System Devices Panel reviewed this application at a public meeting on May 9, 1995, and recommended approval for the Legend Plus® Pacing System. The recommendation for approval was based on Medtronic modifying their labeling to reflect the clinical study's finding with regard to the benefit of the DUAL sensor mode. Specifically, the Panel recommended the following language:

> "Although data from the clinical trial suggest the DUAL sensor mode provides a more physiologic rate response to exercise, no clinical benefit has been demonstrated."

XIII. FDA Decision

FDA completed an inspection of the Medtronic manufacturing facility in Minneapolis, Minnesota on February 15, 1995, and in Humacao, Puerto Rico on May 12, 1995. This inspection determined that the manufacturer was in compliance with the Medical Device Good Manufacturing Practice regulation as defined in 21 CFR 820.

FDA concurred with the above recommendations of the Circulatory System Devices Panel and required Medtronic to make modifications to their labeling consistent with the recommendation of the Panel. Specifically, the FDA in cooperation with Medtronic agreed to the following language and placement:

a. For inclusion on the shelf package:

> "**NOTE:** For important information regarding the clinical evaluation of this device, please refer to Appendix Part 3 - Clinical Abstract, in the Technical Manual,."

b. For inclusion in technical manual chapters 1 (indications) & 2 (description)

> "**NOTE:** Data from the clinical trial do not establish an incremental benefit of the DUAL sensor mode over that achieved by the ACT sensor mode alone, although the DUAL sensor mode appears to provide a rate response to exercise which more closely mimics a normal rate response."

Medtronic amended the application on September 13, 1995, to comply with the Panel recommendation and the FDA requirements.

Subsequent to both the cut-off date for the clinical report and the meeting of the Circulatory System Devices Panel, 2 additional incidents of inappropriate shortening (to the hardware limit of 185 ppm), were noted to have been observed in the field, and further review of patients' ECG strips revealed 3 other occasions with behavior consistent with the events observed in the field. Additionally, periodic Rate limit pacing was reported outside the clinical study in a patient in Canada in January 1995. Medtronic characterized these events as periodic inappropriate Activity pacing occurring in conjunction with appropriate paced events due to MV or intrinsic beats. Medtronic describes this anomalous rate pacing as being attributable to a timing interaction between the telemetry data bits and the controller IC shift clock which shifts those bits into the device registers. The timing between the

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two signals can vary slightly and can result in the corruption of data bits. For the majority of programmed parameters, the result of an incorrect bit would be a "Programming Not Confirmed" message on the programmer after the uplink was sent back to the programmer. However, the mode bits for the activity sensor IC and the minute ventilation IC are held in "shadow" (although programmed in the downlink, they are not echoed in the uplink for verification by the programmer). If either of these bits are read incorrectly, the programmer will not detect the corruption and the pacemaker will be misprogrammed. This can cause one of the sensor ICs to be in "free run" mode, with the result of pacing at activity or MV rate respectively, in addition to rate response based on the other sensor and/or an intrinsic rhythm.. The anomalous pacing can only occur when the device is programmed to a rate adaptive mode.

In response to these events, Medtronic developed a software upgrade which incorporates diagnostic capabilities to allow a user to detect the presence of the misprogramming which allows for "free run" in the Legend Plus®. The software diagnostic is initiated every time the rate responsive modes are programmed and allows the clinician to temporarily program the device to a state in which the presence of "free run" by one or both sensors can be identified. The diagnostic instructs the clinician to program a temporary rate to a value at least 10 beats per minute higher than the prevailing rate. Free run operation will then be evidenced (via Marker Channel trace) by pace-to-pace or sense-to-pace intervals which exceed the programmed temporary rate. Proper programming of a rate responsive rate is demonstrated by intervals which indicate pacing at the programmed temporary rate. If improper intervals are observed by the clinician, he/she is instructed to reprogram the desired rate responsive pacing mode. If proper intervals are observed by the clinician, the diagnostic is exited and the clinician is allowed to continue with their programming session.

XIV. Approval Specifications

Directions for Use: See attached labeling.

Conditions of approval: CDRH approval of this PMA is subject to full compliance with the conditions described in the attached approval order and the Conditions of Approval for Cardiac Pacemakers and Programmers.

Chapter 1. Indications, Warnings, and Precautions

ADVERSE EVENTS

Events Reported During the Clinical Study

POTENTIAL EVENTS

CLINICAL STUDIES

DEVICE DESCRIPTION

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.

Medtronic Legend Plus Models 8446 and 8448 are single chamber, dual sensor (Activity and Minute Ventilation), rate responsive, telemetric, multiprogrammable, lithium-iodine powered, implantable pacemakers. They are intended for permanent pacing applications in either the atrium or the ventricle. The pacemaker can vary the pacing rate based on activity (Activity mode), minute ventilation (MV mode), or activity and minute ventilation (Dual Sensor mode).

NOTE: The Minute Ventilation rate responsive feature operates with either unipolar or bipolar pacing and sensing provided a bipolar lead is used.

Note that a Medtronic programmer is required to interrogate or program the pacemaker. More complete descriptions on using the programmer functions appear in Chapter 3.

INDICATIONS

Legend Plus pacemakers are intended for permanent ventricular or atrial pacing applications. Their use is indicated in the treatment of patients who may benefit from a pacing rate that changes in response to activity.

Ventricular indications include:

- chronic atrial flutter or fibrillation with slow ventricular response
- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, chronotropic insufficiency, etc,)
- AV block

Atrial indications include:

- sinus node dysfunction or sick sinus syndrome (e.g., sinus bradycardia, sinus arrest and/or exit block, bradycardia-tachycardia syndrome, etc,) with intact AV conduction.

NOTE: Data from the clinical trial do not establish an incremental benefit of the dual sensor mode over that achieved by the activity sensor mode alone, although the dual sensor mode appears to provide, for treadmill and bicycle exercise, a rate response which more closely mimics normal physiology (see "Clinical Studies" later in Chapter 1).

CONTRAINDICATIONS

Atrial pacing is contraindicated in the presence of AV conduction disturbances (i.e., pre-existing AV conduction delay or block).

The use of Legend Plus pacemaker for minute ventilation (MV) applications in abdominal placements is contraindicated because MV cannot be accurately measured.

The implantation of the Legend Plus pacemaker is contraindicated with an implantable defibrillator The defibrillator may detect the current pulses that are emitted by the minute ventilation sensor and cause the defibrillator to withhold appropriate therapy or induce inappropriate therapy.

The use of epicardial leads with the Legend Plus pacemaker is contraindicated because the measurement of minute ventilation with epicardial leads has not been demonstrated.

WARNINGS

Rate Responsive Modes

Minute ventilation (MV) rate response pacing may be inappropriate for patients who can achieve respiratory cycles shorter than 1.25 seconds (greater than 48 breaths per minute). In the event that faster respiratory rates occur, the MV sensor-indicated rate gradually diminishes along a 2.5 minute deceleration curve toward the lower rate. For example, a respiratory rate of 60 breaths per minute will result in a sensor rate decrease of 30% of the maximum rate increase. See "Minute Ventilation Rate Responsive Mode Operation" in Chapter 2.

The programming of a rate responsive mode is not properly accepted by the pacemaker in about one out of 1200 mode programmings. The occurrence of this anomaly can produce unexpected variability in the pacing rate, including periodic beats as high as 185 ppm. This situation can occur only when the pacemaker is programmed (or reprogrammed) to a rate responsive mode.

A mode verification test is available to confirm whether or not the programming of rate responsive mode occurred correctly and it is automatically initiated upon programming of a rate responsive mode. See the programmer manual for instructions.

Mechanical Ventilation

The Legend Plus pacemaker may respond to changes induced by mechanical ventilation. To prevent pacing rate changes due to mechanical ventilation, program the pacemaker to a non-MV mode.

Minute Ventilation Lead Requirement

Minute ventilation requires the implantation of a transvenous bipolar lead. The Minute Ventilation rate responsive feature is inoperable when a unipolar lead is used.

An implanted lead with measured impedance greater than 1000 Ohms may result in attenuated Minute Ventilation rate response. When lead impedance is above 3000 ohms, Minute Ventilation rate response will not function. See "Choosing Pacing Configuration and Lead" in Chapter 4.

Using Unipolar Leads

The Legend Plus Models 8446 and 8448 can be connected to unipolar leads. These models do not capture when connected to a unipolar lead and programmed to bipolar pacing. See "Choosing Pacing Configuration and Lead" in Chapter 4.

Asynchronous Pacing Modes

Asynchronous pacing (VOO/AOO or VOOR/AOOR) may be proarrhythmic in the presence of competition between paced and intrinsic rhythms.

High Rate Pacing

High rate stimulation of the ventricle may cause ventricular tachycardia or fibrillation. Application of high rate pacing should be performed only under careful patient monitoring, control, and with defibrillation equipment available. Temporary high rate overrides the rate limit feature, however, it is not available in rate responsive modes.

Electromagnetic Interference

Certain types of electromagnetic interference (EMI) e.g., defibrillation, diathermy, and electrocautery, may damage the pacemaker and/or interfere with its operation, possibly leaving the patient without pacing therapy. See the section "Effects of Electromagnetic Interference" in Chapter 1 for more information.

Electrocautery

Electrocautery units should never be used when replacing a Legend Plus pacemaker. Currents generated from such units may cause a permanent loss of output. See "Hospital and Medical Environment" in Chapter 1.

Magnetic Resonance Imaging

The use of Magnetic Resonance Imaging (MRI) among pacemaker patients has been contraindicated by MRI manufacturers. Medtronic recommends against subjecting pacemaker patients to MRI scanning. Clinicians should carefully weigh the decision to use MRI with pacemaker patients. The following information is provided to the clinician to assist in careful consideration of the risks and benefits of subjecting pacemaker patients to MRI scanning, should the clinical circumstances arise. Limited studies of the effects of MRI on pacemakers have shown that:

- Magnetic and radio frequency (RF) fields produced by MRI may adversely affect the operation of the pacemaker and may inhibit the pacing output.
- Magnetic fields may activate magnet mode operation and cause asynchronous pacing.

Reported[1] effects of MRI on pacing include increased ventricular pacing beyond the rate limit. Pacemaker patients subjected to MRI should be closely monitored and programmed parameters should be verified upon cessation of MRI.

Magnet Usage

Positioning a magnet or the programming head over the pacemaker converts it to asynchronous operation and makes it receptive to programming. **Do not use** electrocautery, diathermy, or any other source of electromagnetic interference in the vicinity of the patient once a magnet or programming head has been positioned over the pacemaker as inadvertent programming may result.

[1] Holmes, Hayes, Gray, et al. The effects of magnetic resonance imaging on implantable pulse generators. *PACE*. 1986; 9 (3): 360-370.

PRECAUTIONS

Pacing Rates for Diagnostic/Pediatric Uses

Carefully monitor the patient when using pacing rates less than 40 or greater than 100 ppm in the demand mode. Rates less than 40 ppm are intended primarily for diagnostic purposes. Programmed rates of 120 to 130 ppm in the inhibited mode are intended for pediatric applications only.

NOTE: Lower Rates in the rate responsive modes are 40, 50, 60, 70, 80 and, 90 ppm. The physician should consider the rate requirements of a pediatric patient when considering the use of the rate responsive modes. With some very young children, the physician may elect to use the VVI/AAI mode to achieve higher pacing rates; then as the child becomes older, program the device to a rate responsive mode at a lower base rate.

Premature Elective Replacement Conditions

Continuous pacing at high rates (> 100 ppm) and at wide pulse widths (up to 1.5 ms) in the demand, or rate responsive modes over a period of several years may cause the battery to indicate elective replacement time. If the battery voltage should temporarily fall to or below 2.5 V, the pacemaker paces at a 10% decrease from the programmed rate in the non-rate responsive mode and at 65 ppm in the rate responsive modes, both without a magnet. While operating at this rate, the battery may gradually recover. If the battery voltage rises above 2.5 V, the pacemaker may be reprogrammed following the battery reset command.

Sterile Package Damage

Inspect the pacemaker sterile package prior to opening; if the seal or package is damaged, contact your local Medtronic representative.

MV Sensor Initialization

The MV Sensor should never be initialized prior to implantation.

The Rate Response Assistant Initialization Protocol should never be started when the device is connected to the Model 5311B Pacing System Analyzer (PSA). The PSA may cause the protocol's impedance interlock to inappropriately allow initialization of the MV Sensor at a pre-implant state. See "Analyzing Pacemaker Operation" in Chapter 4.

The MV Sensor should only be turned ON once the pacemaker is placed securely in the closed subcutaneous pocket. To initialize the MV Sensor, see the Initialization Protocol as described in the programmer manual. If an acute lead requires repositioning, program the MV Sensor OFF prior to repositioning the lead.

Rate Increase Caused by "Twiddler's Syndrome"

"Twiddler's syndrome," i.e., patient manipulation of the device after implant, may cause the pacing rate to increase temporarily, if the device is programmed to a rate responsive mode.

Effects of Pressure in the Activity Mode

Clinical studies on the rate responsive, activity-detecting pacemakers have reported instances of increased sensitivity of the pacemaker to muscle motion (such as heart contractions) when external pressure is exerted on the device. Tests reveal a gradual increase in the pacing rate, but not up to the programmed Upper Activity Rate at **nominal settings** (Activity Threshold = Medium, Activity Rate Response = 7, Lower Rate = 60 ppm, Upper Activity Rate = 120 ppm). This might occur when the patient is lying on the pacemaker while sleeping, or by pressing the programmer head to activate the "Cancel Magnet" function over the pacemaker with the patient supine. Implantation of the pacemaker near the patient's skeletal system (e.g., in a very thin patient), may augment the effect when pressure is applied. This phenomenon does not indicate device malfunction or inappropriate programming. Relief of pressure on the implanted device should result in the pacing rate returning to the appropriate rate. Reprogramming the Activity Threshold to a higher setting reduces the effects of pressure and the potential for a rate increase.

Muscle Stimulation in the Activity Mode

Under certain circumstances (e.g., high output settings, a break in the device's insulative coating, etc.), the pacemaker can induce muscle stimulation at the pocket site. If this occurs with the Legend Plus Models 8446 or 8448 in the unipolar polarity (when programmed to an Activity mode), the muscle contractions may be detected by the Activity sensor. Such detection, in turn, may result in a rise in pacing rate. The extent of rate elevation is dependent on the programmed Activity Rate Response setting, i.e., the higher the setting, the higher the pacing rate.

In such cases and at **nominal settings** (Activity Threshold = Medium, Rate Response = 7, Lower Rate = 60 ppm, Upper Rate = 120 ppm), the pacing rate remains below 110 ppm in a **resting patient.**

NOTE: Higher rates may occur at other settings such as Activity Threshold = Medium, Activity Rate Response = 10, Lower Rate = 90 ppm, Upper Activity Rate = 170 ppm. Upon termination of pacer-induced muscle stimulation, the pacing rate returns to its Lower Rate or to that level which corresponds to the activity being detected (i.e., nonpacer-induced). In most circumstances, muscle stimulation may be effectively controlled and/or alleviated by reducing the programmed amplitude or pulse width.

Effects of Electromagnetic Interference

The Legend Plus pacemaker is immune to sensing common sources of electromagnetic interference (EMI). Various EMI sources exist or could become common in the future. The following paragraphs contain information on typical EMI sources within the hospital, medical, home, and job environments. Additional information on the behavior of the pacemaker in the presence of EMI is available upon request.

NOTE: In the presence of EMI, the pacemaker may become inhibited, pace to the Upper MV Rate in MV rate responsive modes, or revert to asynchronous pacing. Turn off the EMI source or move away from the source to return the pacemaker to its normal operation. Some types of EMI may reset the programmed settings.

Hospital and Medical Environment

Defibrillation

The pacemaker may be damaged by defibrillatory charges, possibly causing loss of pacing. In addition, defibrillatory discharges may result in temporary and/or permanent myocardial damage at the electrode-tissue interface or temporary and/or permanent elevated pacing thresholds.

To reduce the risk of damaging the device, place defibrillation paddles at least 12 cm (5 inches) from the pacemaker and confirm pacemaker function following defibrillation. Defibrillatory charges may cause an electrical reset of the device or set the elective replacement indicators. (See "Elective Replacement Indicators" and Electrical Reset Parameters" in the Appendix for parameter settings and instructions.)

Diathermy

Therapeutic diathermy should not be used directly over a pacemaker since internal components may be damaged by heating.

Electrocautery

The electrocautery tip should never be used in the vicinity of [15 cm (6 inches) or closer] an implanted Legend Plus pacemaker/lead system. (See "Pacemaker Replacement" in Chapter 5.)

The use of electrocautery:

- **can induce ventricular fibrillation,**
- **may cause permanent loss of output in either electrode configuration,**
- **may cause the pacing rate to rise to the Upper MV or Upper Activity Rate limit,**
- **may inhibit pacing output or revert the pacemaker to asynchronous operation, and**
- **may cause the pacemaker to go to electrical reset or elective replacement conditions. (See the sections on "Elective Replacement Indicators" and "Electrical Reset Parameters" for parameter settings and instructions.)**

The required level for such effects varies with the type of electrocautery unit, coagulation and cutting current settings, current pathway from the cautery tip to indifferent plate, and pacemaker/lead system.

Because of all these potential complications, an **alternative to electrocautery should be used, where available.** Care must be taken to minimize the potential for any of the conditions described above when using electrocautery.

If using electrocautery is necessary, it is recommended that:

1. The device be programmed to the asynchronous mode (VOO/AOO).
2. The current path from the cautery electrode tip to indifferent plate should be kept as far away from the pacemaker/lead system as possible (e.g., the ground plate be located under the patient's buttocks or legs during abdominal surgery).
3. Short, intermittent, and irregular bursts at the lowest feasible energy levels be used.
4. Where possible, a bipolar electrocautery unit be used.
5. Temporary pacing and defibrillation equipment be readily available.

NOTE: Electrocautery units could also interfere with electrocardiographic monitoring equipment. If such devices are used on patients, cardiac activity should be followed by continuous palpation of the peripheral pulse or by monitoring of the peripheral arterial or intraventricular pressure.

External Monitoring Equipment

Electrical current applied across the patient's thorax by external monitoring equipment, such as a respiration rate monitor, may affect the pacing rate in minute ventilation (MV) rate responsive modes. The current may be detected by the pacemaker's MV sensor, which may result in the pacing rate increasing up to the programmed Upper MV Rate. If external monitoring equipment is used, program the pacemaker to a non-MV mode prior to turning the equipment on.

Irradiation

The pacemaker should not be directly irradiated by therapeutic levels of ionizing radiation (such as produced by cobalt machines or linear accelerators used for cancer treatment) because of the risk of permanent damage to the pacemaker circuitry. If such therapy is required in the vicinity of the pacemaker, the pacemaker should be shielded and its function confirmed following treatment.

Lithotripsy

Permanent damage to the pacemaker may occur if the pacemaker is at the focal point of the lithotripsy beam. Since this situation is easily avoided, lithotripsy may be used provided:

1. The pacemaker is programmed to the VVI/AAI or VOO/AOO mode prior to treatment.
2. The pacemaker is further than 5 cm (2 inches) away from the focal point of the lithotripsy beam.

X-Ray and Fluoroscopy

Controlled exposure to diagnostic X-ray and fluoroscopic radiation has not affected the Legend Plus pacemaker.

Home or Job Environment

Based on laboratory tests of the Legend Plus pacemaker, the device should not be affected by the normal operation of electrical equipment such as household appliances, electric machine shop tools, microwave ovens, spark-ignited internal combustion engines, low-powered radio frequency transmitting systems or low-powered microwave frequency transmitting systems. All such equipment should be kept in good repair and properly grounded to avoid the possibility of electrical shock or interference with the proper operation of the pacemaker.

Some types of theft prevention equipment, such as those found at store entrances and exits, may temporarily inhibit the Legend Plus pacemaker or cause it to revert to asynchronous operation. The pacemaker returns to normal operation when the patient moves away from such equipment.

Medtronic should be consulted when the pacemaker wearer will be in areas where contact with current carrying conductors is possible or near high-powered electromagnetic fields radiated by arc welding units, induction furnaces, induction stoves, resistance welders, radio, or microwave frequency transmitters, etc.

Cellular Phones

Recent studies have indicated there may be a potential interaction between cellular phones and pacemaker operation. Potential effects may be due to either the radio frequency signal or the magnet within the phone and could include inhibition or asynchronous pacing when the phone is in close proximity (within 6 inches or 15 cm) to the pacemaker.

Based on testing to date, effects resulting from an interaction between the cellular phone and the implanted pacemaker have been temporary. Simply moving the phone away from the implanted device will return it to its previous state of operation. Because of the great variety of cellular phones and the wide variance in patient physiology, an absolute recommendation to cover all patients cannot be made.

Patients having an implanted pacemaker who operate a cellular phone should:

- Maintain a minimum separation of 6 inches (15 cm) between a hand-held personal cellular phone and the implanted device. Portable and mobile cellular phones generally transmit at higher power levels compared to hand-held models. For phones transmitting above 3 watts, maintain a minimum separation of 12 inches (30 cm) between the antenna and the implanted device.
- Patients should hold the phone to the ear opposite the side of the implanted device. Patients should not carry the phone in a breast pocket or on a belt within 6 inches (15 cm) of the implanted device as some phones emit signals when they are turned ON but not in use (i.e., in the listen or standby mode). Store the phone in a location opposite the side of the implant.

ADVERSE EVENTS

EVENTS REPORTED DURING THE CLINICAL STUDY

The clinical investigation of the Legend Plus pulse generator involved 262 devices implanted in 262 patients for a total of 4106 cumulative device months of experience (mean = 15.7 months). Sixteen patients died during the course of the clinical study. None of the deaths were judged to be related to the device. Adverse events (AEs) including 2 complications and 89 observations were reported during the clinical investigation. Table 1 reports these data on a per patient and a per patient-month basis.

Subsequent to closing the clinical trial, instances of anomalous pacing behavior were noted. This behavior, indicated by unexpected variability in the pacing rate, was determined to occur in approximately 1 in 1,200 mode programmings, wherein the programmed rate response mode information is not correctly accepted by the pacemaker.

Warning: The programming of a rate responsive mode is not properly accepted by the pacemaker in about one out of 1200 mode programmings. The occurrence of this anomaly can produce unexpected variability in the pacing rate, including periodic beats as high as 185 ppm. This situation can occur only when the pacemaker is programmed (or reprogrammed) to a rate responsive mode.

A mode verification test is available to confirm whether or not the programming of a rate responsive mode occurred correctly and it is automatically initiated upon programming of a rate responsive mode. See the programmer manual for instructions.

Table 1. Adverse Events

Type of AE	# of Patients (n=262)	% of Patients	# AEs	AE/ Pt-Mo (n=4106)	Pt. Mos Between AEs
Observations[1] (89)					
Inappropriate Programming	42	16.03%	51	.0124	81
Hematoma/Seroma	8	3.05%	8	.0019	513
Pacemaker Syndrome	5	1.91%	5	.0012	821
Pain/Swelling at Pocket Site	4	1.53%	4	.0010	1027
Failure to Capture	3	1.15%	3	.0007	1369
Pain/Swelling at Angina	2	0.76%	2	.0005	2053
Failure to Sense	2	0.76%	2	.0005	2053
Inadequate Cardiac Output	2	0.76%	2	.0005	2053
Inappropriate Rate Response	2	0.76%	2	.0005	2053
Local Infection at Pocket	2	0.76%	2	.0005	2053
Pacemaker Migration	2	0.76%	3	.0007	1369
Fatigue	1	0.38%	1	.0002	4106
Fluttering at Pocket Site	1	0.38%	1	.0002	4106
Systemic Infection	1	0.38%	1	.0002	4106
Tachycardia	1	0.38%	1	.0002	4106
Ventricular Oversensing	1	0.38%	1	.0002	4106
Complications[2] (2)					
Inappropriate Device Operation	1	0.38%	1	.0002	4106
Pacemaker Migration	1	0.38%	1	.0002	4106

[1] Observations are adverse events which are correctable by noninvasive measures, e.g., reprogramming.

[2] Complications are adverse events requiring invasive measures to correct, e.g., surgical intervention.

POTENTIAL EVENTS

Potential events not seen during the clinical trial, but commonly associated with cardiac pacing include, but are not limited to, body rejection phenomena including local tissue reaction, fibrotic tissue formation, muscle and nerve stimulation, infection, erosion of pacemaker lead through skin, myopotential sensing, transvenous lead-related thrombosis, embolism, and cardiac tamponade. (See also "Potential Events" in Table 2.)

Table 2. Potential Events

Component	Condition	Possible Event
Power Source	Premature depletion due to high internal losses	Output voltage decrease, no output, loss of capture, reversion to elective replacement parameters, shortened time interval after elective replacement indicator is set.
Other Components	Electrical parameter changes due to shorts, open circuits or shifts in component parameters.	No output, rate change, reversion to asynchronous mode, loss of capture, loss of programming function, changes in parameter settings, reversion to elective replacement or electrical reset parameters.*
Circuitry	Electromagnetic interference (EMI) from power tools, equipment, appliances, etc.	Output inhibition, pace to the Upper MV Rate in MV modes, reversion to asynchronous mode, pacing synchronized to interference, reversion to reset parameters.*
	EMI from electrocautery	Permanent loss of output, output inhibition, reversion to asynchronous mode and rate change or instability, pace to the Upper MV Rate in MV modes, reversion to reset or elective replacement parameters.*
	EMI from defibrillator	Permanent loss of output, reversion to reset parameters.*
Connector	Poor Connection	Intermittent or continuous loss of capture, failure to sense properly.

* See "Electrical Replacement Indicators" and "Electrical Reset Parameters" in the Appendix for more information.

Table 2. Potential Events (continued)

Component	Condition	Possible Event
Leads	Displacement or fracture	Intermittent or continuous loss of capture and/or sensing, inhibition of ventricular output.
		Minute ventilation detection ceases and lower rate pacing begins.
	Cardiac perforation	The above events, plus cardiac tamponade, muscle or nerve stimulation.
	Myocardial irritability at time of insertion	Fibrillation, flutter.
	Pacing threshold elevation	Loss of Capture.
Activity Sensor	Open or short circuit	Activity detection ceases and lower rate pacing begins.
	Inappropriate detection, e.g., muscle stimulation, external mechanical stimulation, etc.	Rise in pacing rate, potentially to levels higher than expected or desirable.
Minute Vent. Sensor	Open or short circuit	Minute ventilation detection ceases and lower rate pacing begins.
	Inappropriate detection, e.g., upper body motion.	Rise in pacing rate, potentially to levels higher than expected or desirable.

CLINICAL STUDIES

Crossover comparison of Activity (ACT), Minute Ventilation (MV), and Dual Sensor (DUAL) mode pacing using the Medtronic Legend Plus Pacemaker System.

Primary Objectives: To demonstrate the safety of the Legend Plus pacemaker and the utility of the measurement of transthoracic impedance to estimate minute ventilation for use as a rate response sensor and in combination with the activity sensor (DUAL) as a rate response sensor.

Methods: The Legend Plus pacemaker system was studied in 262 patients with indications for single chamber pacing for 4,106 device months at 24 U.S. and 22 non-U.S. centers. Chronotropic incompetence (CI) was demonstrated in 123 of 171 patients (72%) assigned to a randomized three mode (ACT, MV and DUAL crossover study with specialized testing during the Intensive Phase (3 months, 1 test per month). Safety Assessment was based on the exposure of all patients.

Table 3. Clinical Results

Principal Effectiveness and Safety Results Based on Selected Chronotropically Incompetent Patients, Mean ± Std. Dev.

Test	N	ACT	MV	DUAL	Difference
Treadmill Exercise Duration	60	13 min. ± 3	13 min. ± 3	13 min. ± 3	
Treadmill Time to Anaerobic Threshold	24	11 min. ± 3	11 min. ± 3	11 min. ± 3	
Treadmill Percent of Upper Rate*	60	85% ± 13	90% ± 14	93% ± 12	MV & DUAL > ACT
Bicycle Exercise Duration	30	9 min. ± 3	9 min. ± 3	9 min. ± 3	

* Note absence of correlation to measured physiologic benefit.

Table 3. Clinical Results (continued)

Principal Effectiveness and Safety Results Based on Selected Chronotropically Incompetent Patients, Mean ± Std. Dev.

Test	N	ACT	MV	DUAL	Difference
Bicycle Time to Anaerobic Threshold	16	7 min. ± 3	7 min. ± 2	7 min. ± 2	
Bicycle Percent of Upper Rate [a]	30	72% ± 14	88% ± 16	89% ± 15	MV & DUAL > ACT [b]
Treadmill O_2 Deficit	16	663 ml/min. ± 315	912 ml/min. ± 421	656 ml/min. ± 251	ACT & DUAL < MV [c]
Treadmill Mean Response Time	16	56 sec. ± 15	73 sec. ± 21	57 sec. ± 21	ACT & DUAL < MV [d]
Difference in Treadmill Heart Rate for 1st Minute	48	27 ppm ± 15	16 ppm ± 17	26 ppm ± 14	ACT & DUAL > MV [b]

Safety Results	ACT		MV		DUAL		SSI	
Exposure Months	597		326		2986		118	
Number of Patients	155		127		244		256	
	N	%	N	%	N	%	N	%
Clinical Complications	0	0	0	0	2	0.8	0	0
Clinical Observations	12	7.7	12	9.4	42	17.2	13	5.1
Deaths e	3	2	1	0.8	8	3	4	2

Results: The O_2 kinetics testing during a constant workload test demonstrated that the two modes involving the ACT Sensor (ACT and DUAL) provided a quicker chronotropic response and a lesser O_2 deficit at the onset of exercise than did the MV Sensor alone ($p < 0.02$). The difference in the percentage of the minimum programmed heart rate achieved during maximum treadmill and bicycle testing involving the MV sensor (MV and DUAL) is statistically significant ($p < 0.001$), however, this does not correlate with a measured physiological benefit. Time to anaerobic threshold and exercise duration time did not differ statistically among the three modes (ACT, MV, and DUAL).

Conclusion: Data from the clinical trial do not establish an incremental benefit of the Dual Sensor mode over that achieved by the Activity Sensor mode alone, although the Dual Sensor mode appears to provide, for treadmill and bicycle exercise, a rate response which more closely mimics normal physiology.